Benzotriazole-mediated amidoalkylations of nitroalkanes, nitriles, alkynes and esters

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Abstract

Reactions of readily available and stable *N*-(*α*-amidoalkyl)benzotriazoles **1** (derived from a variety of aliphatic, aromatic or heterocyclic aldehydes) with diverse nitroalkanes, nitriles, alkynes and esters afforded *N*-(*β*-nitroalkyl)amides **4** (54–96%), *N*-(*β*-cyanoalkyl)amides **6** (58–88%), *N*-acylpropargylamines **11** (41–87%) and esters of *β*-*N*-acylamino acid**s 13** (68–96%), respectively.

Keywords: Amidoalkylation, *N*-(*β*-nitroalkyl)amides, *N*-(*β*-cyanoalkyl)-amides, *N*-acylpropargylamines, *β*-*N*-acylamino acids

Introduction

Amidoalkylations have attracted attention in organic synthesis as a valuable alternative to the Mannich reaction [1] since they provide ready access to a wide variety of *α*-substituted amines.[2] Amidoalkylation of π-nucleophiles, including alkenes, allenes, alkynes and (hetero)aromatic systems, is a common step in the synthesis of nitrogen heterocycles,[2a,b] alkaloids,[3] and other nitrogen-containing biologically active compounds.[2b] Intramolecular amidoalkylations have been applied to the synthesis of monocyclic,[4] bicyclic and polycyclic systems with stereocontrol.[5]

Benzotriazole mediated amidoalkylations introduced in 1988,[6] offer advantages over previously reported methods as was already demonstrated for the amidoalkylation of (i) Grignards,[6] (ii) malonates and acetoacetates,[7] (iii) cyanide anion,[8] (iv) mercaptans and alcohols,[9] (v) electron-rich (hetero)aromatics,[10] and (vi) amines [11] (Scheme 1).

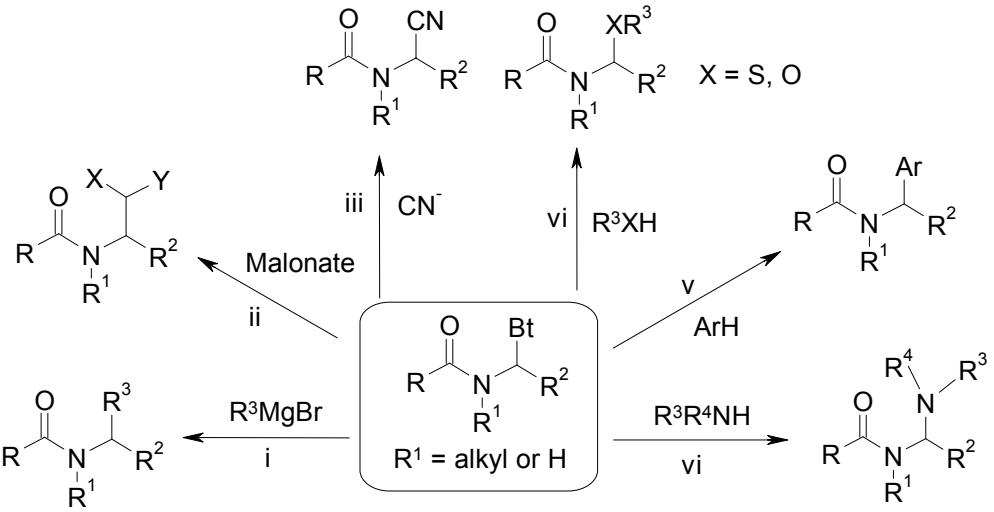
[*] Alan Katritzky was Chairman of the RSC Heterocyclic Group during the period 1967-1969.

We now report that *N*-(α-amido-alkyl)benzotriazoles are also advantageous for the amidoalkylation of nitroalkanes, nitriles, acetylenes, and esters to produce the corresponding novel *β*-functionalized amides.

Results and Discussion

Preparation of *N*-(*α*-amidoalkyl)benzotriazoles 1a–i

Amidoalkylation reagents **1a–i** were easily prepared by the well-established condensation of benzotriazole, an aldehyde, and an amide in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene with azeotropic removal of water.[12] Both aliphatic and aromatic aldehydes gave stable products **1** in good yields, which were fully characterized on the basis of their ^{1}H and ^{13}C NMR spectra and elemental analyses. The ^{1}H and ^{13}C NMR spectra of these *N*-(α-amidoalkyl)benzotriazoles confirmed that the products **1a–i** are all benzotriazol-1-yl compounds with no isomerization to benzotriazol-2-yl isomers.



Scheme 1

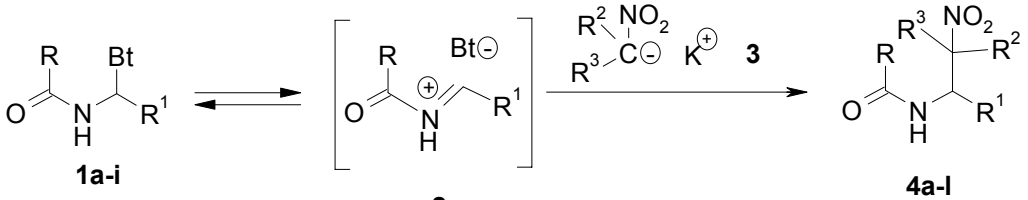
Synthesis of *N*-(*β*-nitroalkyl) amides

Nitronate salts act as carbon nucleophiles in the well-known Michael,[13] Henry,[14] Knoevenagel,[15] and nitro-Mannich reactions,[16] providing valuable derivatives in which the nitro group can be retained, reductively eliminated, or transformed to provide ketones,[17] amines,[18] oximes,[19] or nitriles.[20] Therefore, methodologies to introduce the nitro group into a molecular framework along with other functionalities have gained momentum.

N-(*α*-Amidoalkyl)benzotriazoles **1** (R^1 derived from benzaldehyde) react with sodium alkanenitronates in DMF.[21] Encouraged by reports that *N*-(*β*-nitroalkyl)amides of type **4** represent viable intermediates to *N*-protected *α*-amino acids,[22] we have now generalized this efficient entry to *N*-(*β*-nitroalkyl)amides (Scheme 2).

Reacting **1f** with 2 molar equivalents of potassium methanenitronate, generated *in situ* gave *N*-(*β*-nitroalkyl) amide **4a** (79%), we note that neither NaH nor $NaOCH_3$ promote this reaction. The scope of the reaction is wide: *N*-(α-amidoalkyl)benzotriazoles derived from aliphatic, aromatic, and heteroaromatic aldehydes and various primary amides, were reacted with diverse nitroalkanes to provide the corresponding *β*-nitroalkyl amides **4a–l** (Scheme 2 and Table 1).

Formation of the nitroamides of type **4** is indicated by the loss of benzotriazole signals in ^1H and C^{13} NMR. In the ^{13}C NMR spectra of the compounds **4**, resonances arising from amide carbonyl and carbons adjacent to the nitro group are found in the regions of 166.3–178.2 ppm and 86.0–97.0 ppm, respectively and their structures were also confirmed by elemental analysis.



1a: R = Ph, R^1 = H
1b: R = Ph, R^1 = Isopropyl
1c: R = Ph, R1 = Isobutyl
1d: R = Ph, R^1 = *t*-$BuCH_2$
1e: R = Ph, R^1 = *p*-Tolyl
1f: R = Ph, R^1 = 1-Naphthyl
1g: R = $CH_3(CH_2)_7CH_2$, R^1 =*p*-Tolyl
1h: R = CH_3, R^1 = 2-Thienyl
1i: R = *t*-Bu, R1 = 3-Pyridyl

For designation of R, R^1 R^2 and R^3 in **4** see Table 1

Scheme 2

Table 1. Preparation of *N*-(*β*-nitroalkyl) amides **4a–l**

Compd	R	R^1	R^2	R^3	Yield %
4a	Ph	*p*-Tolyl	H	H	79
4b	Ph	*p*-Tolyl	CH_3	CH_3	82
4c	Ph	Isopropyl	H	H	85
4d	Ph	Isopropyl	CH_3	CH_3	87
4e	Ph	Isopropyl	H	Et	96
4f	Ph	H	H	H	54
4g	Ph	H	CH_3	CH_3	86
4h	Ph	Isopropyl		$(CH_2)_5$	93
4i	$CH_3(CH_2)_8$	*p*-Tolyl	H	CH_3	89
4j	Ph	*t*-$BuCH_2$	H	CH_3	81
4k	CH_3	2-Thienyl	H	Et	58

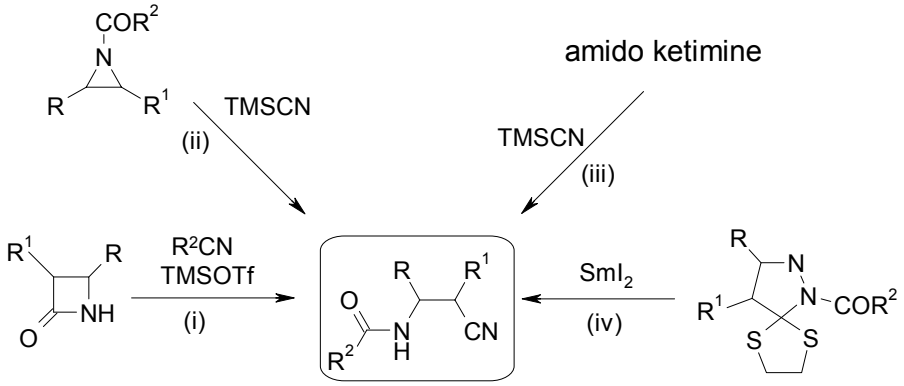
4l	*t*-Bu	3-Pyridyl	H	Et	60

Previous approaches to *N*-(*β*-nitroalkyl) amides include: (i) nitroacetamidation of olefins by $NaNO_2$-ceric ammonium nitrate-acetonitrile reagent [23] (examples limited to cyclic olefins); (ii) nucleophilic substitution of α-bromoalkyl amides with lithium alkanenitroates [24] (examples limited to *α*-bromoglycine derivatives); and (iii) reactions of sodium nitronate with α-amidoalkyl sulfones [22b] (examples limited the amidoalkylation of nitromethane). The previously described protocol can tolerate variation in each component; the 12 examples of Table 1 demonstrate that *N*-(*α*-amidoalkyl)benzotriazoles derived from formaldehyde, aliphatic, aromatic or heterocyclic aldehydes and diverse amides can amidoalkylate primary and secondary nitroalkanes providing the expected *β*-nitroalkyl amides in yields ranging from 54% to 96% (average 77%).

Synthesis of *N*-(*β*-cyanoalkyl)amides

β-Amino acids and their derivatives show a variety of interesting biological properties.[25] Therefore, a new strategy for *N*-(*β*-cyanoalkyl)amide synthesis can provide valuable intermediates for *β*-amino acids.[26]

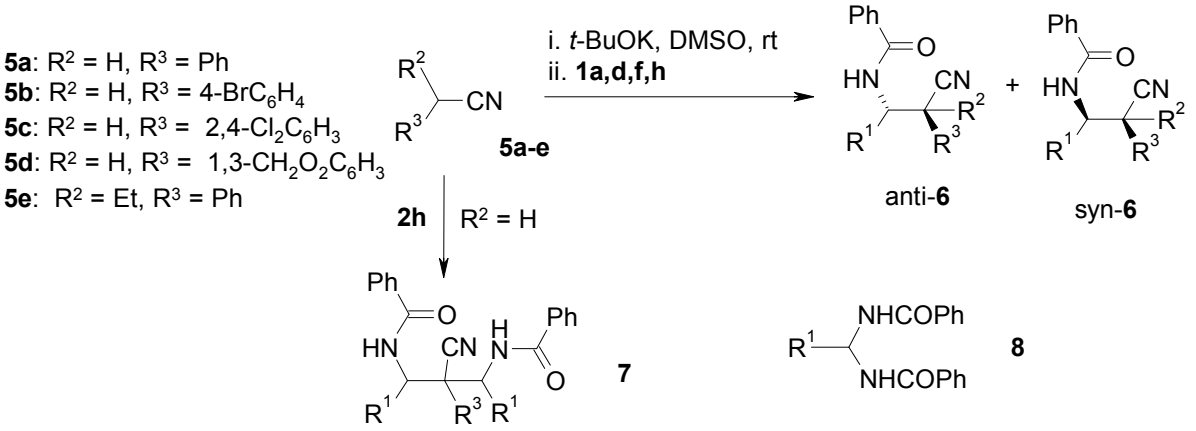
N-(β-Cyanoalkyl)amides were previously prepared (Scheme 3): (i) by 2,3-bond cleavage of azetidinones promoted by trimethylsilyl trifluoromethanesulfonate (TMSOTf) in a cyano group-containing solvent; [27] (ii) nucleophilic ring opening of *N*-acyl aziridines with trimethylsilyl cyanide (TMSCN) triggered by tetrabutylammonium fluoride;[28] (iii) Lewis acid-catalyzed cyanide addition of α-iminoalkyl amide using trimethylsilyl cyanide (TMSCN);[26b] and (iv) N-N bond cleavage of pyrazolidine derivatives having a thioketal moiety with SmI_2.[29] However, none can be considered a general methodology; overall methods (i) – (iv) report a total of just nine examples. Recently, we reported reactions of metallated nitriles with *N*-sulfonyl-,[30] *N*-acyl-,[31] and *N*-(*α*-aminoalkyl)benzotriazoles [32] to provide novel approaches to cyano- sulfones, ketones and amines, respectively. We now disclose a logical extension of this synthetic strategy by the utilization of *N*-(*α*-amidoalkyl)benzotriazoles as electrophilic substrates for metalated nitriles.



Scheme 3

Trials with different base-solvent couples disclosed that phenylacetonitrile treated with 1.2 molar equivalent of *t*-BuOK in DMSO followed by subsequent addition of *α*-(amidoalkyl)benzotriazole **1a** solution in DMSO at 15 °C provided 58% of the amidomethylated product **6a**. The significant acidity of the hydrogen linked to the nitrogen atom in **1** and anion-exchange explains the bis-amide **8** byproduct.

Using these optimized conditions, potassio-derivatives of **5a–e** (generated from primary or secondary nitriles) reacted with diverse **1** to give 10 examples of the expected mono-amidoalkyation products **6** in yields 61% to 92% (Scheme 4 and Table 2). For *β*-amidoalkyl nitriles **6** containing two asymmetric carbon atoms, the reaction shows little stereoselectivity; in nearly all cases two stereoisomers were isolated in about 1:1 ratio. Assignment of the two stereoisomers as *syn* and *anti* was accomplished by utilizing the reasoning of Carlier et al on *β*-hydroxy nitriles,[33] and our own recent results with *β*-aminoalkyl nitriles.[32] The reaction of **1h** with **5c** under the same conditions provided the doubly amidoalkylated product **7** (46%) (Scheme 4, Table 2).



For designation of R^1 R^2 and R^3 in **6** and **7** see Table 2.

Scheme 4

Table 2. Synthesis of *β*-cyanoalkyl amides **6** and **7**

Compd	R^1	R^2	R^3	Yield % of *anti-6*	Yield % of *syn-6*	Overall yield %
6a	*t*-BuCH_2	H	Ph	78	-	78
6b	*t*-BuCH_2	H	4-BrC_6H_4	87	-	87
6c	*t*-BuCH_2	H	Ben[a]	45	41	86
6d	*t*-BuCH_2	Et	Ph	45	43	88
6e	1-Naphthyl	Et	Ph	41	32	73
6f	H	H	Ph	-	-	58
6g	H	H	2,4-$Cl_2C_6H_3$	-	-	65

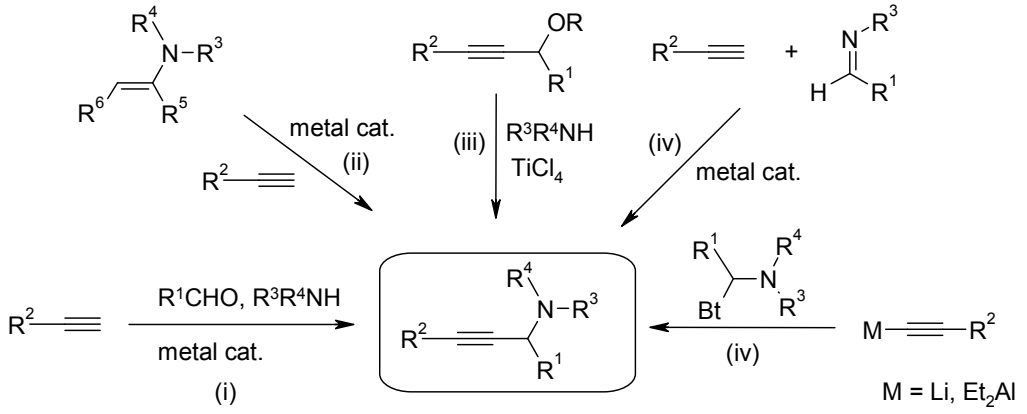
6h	H	Et	Ph	-	-	61
7	1-Naphthyl	-	2,4-$Cl_2C_6H_3$		-	44

[a]1,3-Benzo[1,3]dioxol-4-yl

Novel structures of **6** and **7** were supported by their elemental analyses and spectral data. The ^{13}C NMR spectra of the amides show the absorption peak for the carbonyl group in the region of 168.4–166.8 ppm and for the carbon directly attached to the amide nitrogen at 56.1–53.1 ppm.

Synthesis of *N*-acylpropargylamines

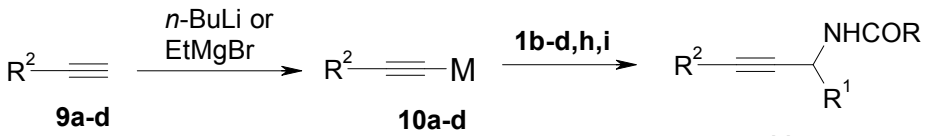
Propargylamines are important therapeutic agents:[34] inhibitors of monoamine oxidase B and aldehyde dehydrogenase enzymes [35] and potential antifungal agents.[36] They are also precursors for allylic amines and other targets.[37] Propargylamines were previously prepared by: (i) metal-catalyzed three-component coupling of aldehyde, alkyne, and secondary amine;[38] (ii) metal-catalyzed addition of alkynes to enamines;[39] (iii) $TiCl_4$-mediated amination of propargylic esters;[40] (iv) transition metal promoted addition reaction of terminal alkynes to imines;[41] and (v) alkynylation of *N*-(*α*-aminoalkyl)benzotriazoles with lithium alkynides [42] or dialkynyl-diethylaluminates [43] (Scheme 5). We now report the synthesis of *N*-acyl-*α*-propargylamines **11** (Scheme 6)**,** which can serve as precursors for the corresponding *α*-propargylamines.[40]



Scheme 5

2-Phenylacetylene **9a** was treated with 1.2 equiv. of *n*-BuLi to give **10a** *in situ* which on treatment with **1c,d** at -78 ^oC in THF afforded 53% and 63% of **11a** and **11b**, respectively. The molar equiv. of lithium alkynide could be replaced by 1.9 equiv. of alkynylmagnesium bromide **10** (prepared by treating **9** with 1.65 equiv of EtMgBr) at rt affording the corresponding *N*-acylpropargylic amides **11c–g** in 47–87% yields (Scheme 6 and Table 3). Structures **11c–g** were characterized by NMR spectroscopy. The ^1H NMR of **11** showed the characteristic peak of NH

as doublet in the region 6.20–6.41 ppm and the peaks of the two acetylenic carbons appeared in the ^{13}C NMR spectra in the regions 83.7–88.7 ppm and 76.4–84.3 ppm.



9a: R^2 = Ph; **9b**: R^2 = *p*-Tolyl
9c: R^2 = *n*-Pentyl; **9d**: R^2 = *n*-Hexyl

For designation of R, R^1 and R^2 in **11** see Table 3.

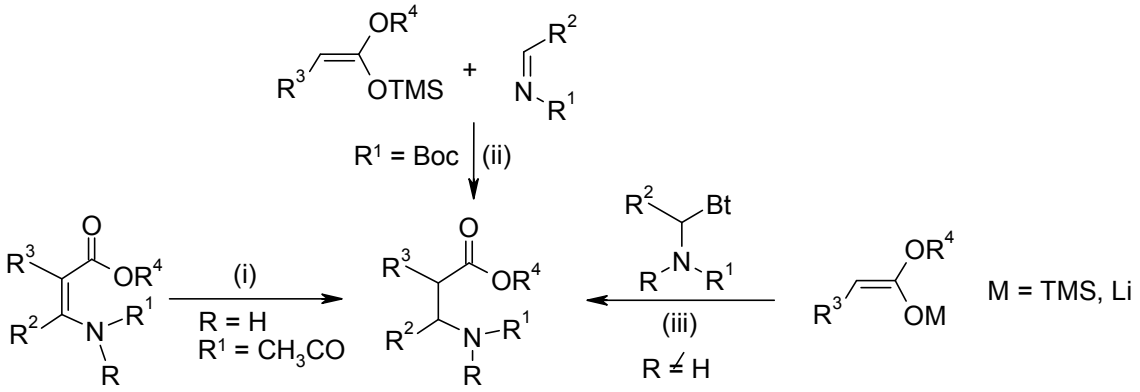
Scheme 6

Synthesis of esters of *β*-*N*-acylamino acids 13

β-Amino carbonyl compounds are precursors for biologically important *β*-lactams and *β*-amino acids.[44] Therefore, a number of synthetic pathways have been devised for their preparation including (Scheme 7), (i) enantioselective hydrogenations of *β*-amine acrylate;[45] (ii) asymmetric additions of different enolate equivalents to imines;[46] and (iii) reactions of *N*-(α-aminoalkyl)benzotriazoles with ketene silyl acetals catalyzed by either lanthanide triflate [47] or methyl lithium.[48] We now report that reaction of esters with **1** provides a novel access to *β*-*(N*-protected-amino)alkyl esters **13** (Scheme 8).

Table 3. Synthesis of *N*-acyl propargylic amines **11**

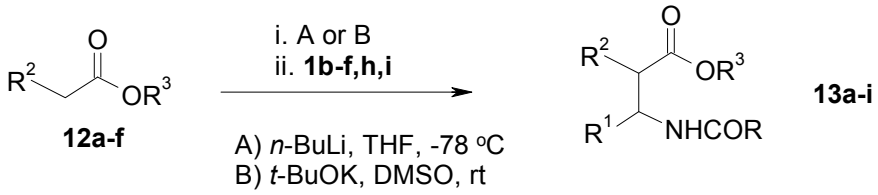
Compd	R	R^1	R^2	M	Yield %
11a	Ph	*t*-BuCH_2	Ph	Li	53
11b	Ph	Isobutyl	Ph	Li	63
11c	4-Tolyl	Isobutyl	Ph	MgBr	86
11d	4-Tolyl	Isopropyl	Ph	MgBr	85
11e	*n*-Pentyl	Isobutyl	Ph	MgBr	80
11f	n-Hexyl	2-Thienyl	CH_3	MgBr	41
11g	Ph	3-Pyridyl	*t*-Bu	MgBr	87



Scheme 7

Reactions of lithium or potassium enolates, prepared *in situ* by treating the corresponding ester itself **12a−c** with LDA in THF or *t*-BuOK in DMSO, with **1b−d** provided *β-(N*-protected-amino)alkyl esters **13a−e** in moderate to excellent yields (Scheme 8 and Table 4).

Previously malonates and acetoacetates [7] were reacted with **1** in the presence of anhydrous aluminum chloride and gave the amidoalkyated products of type **13** in moderate yields. The efficiency of the nucleophilic substitution of benzotriazole from compounds of type **1** is demonstrated by comparison of the electrophilic conditions. Ethyl benzoylacetate (**12d**), methyl and benzyl acetoacetate (**12e,f**), and ethyl malonate (**12g**), each reacted efficiently with **1** in the presence of 1.2 equiv. *t*-BuOK in DMSO at rt, to give the amidoalkylated derivatives **13f−h** (84−96%) (Scheme 7 and Table 4). The ^{1}H NMR spectra of **13** showed that while **13c** and **13d** were diastereomeric mixtures **13a,b** and **13e−g** were single diastereomers. In the ^{13}C NMR spectra of **13** the characteristic signals of ester and amide carbonyls appeared at 172.6−173.2 ppm and 167.2−169.2 ppm.



For designation of R, R^1, R^2 and R^3 in **13** see Table 4.

Scheme 8

Table 4. Synthesis of esters of *β-N*-acylamino acid**s 13**

Compd	R	R^1	R^2	R^3	Method	Yield %
13a	Ph	*t*-BuCH_2	Ph	Me	A	68
13b	Ph	Isobutyl	1-Naphthyl	Me	B	92
13c	Ph	Isopropyl	1-Naphthyl	Me	B	89

13d	Me	2-Thienyl	Ph	Me	B	75
13e	Ph	*t*-BuCH_2	PhCO	Et	B	84
13f	Ph	*p*-Tolyl	CH_3CO	Me	B	88
13g	Ph	1-Naphthyl	CH_3CO	Bn	B	96

In summary, we have developed convenient approaches for *N*-(*β*-nitroalkyl)-amides**,** *N*-(*β*-cyanoalkyl) amides, *N*-acylpropargylamines and esters of *β*-*N*-acylamino acid**s** by the amidoalkylation of nitroalkanes, nitriles, alkynes, and esters and *β*-keto esters with *N*-(*α*-amidoalkyl)benzotriazoles. The adopted procedures are simple and applicable to the preparation of amidoalkylation products derived from formaldehyde, aliphatic, and (hetero) aromatic aldehydes. In all cases, the *N*-protected amine derivatives were produced in high yields that make the use of *N*-(*α*-amidoalkyl)benzotriazoles as *N*-acyliminium ion equivalents advantageous.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of nitrogen, unless otherwise specified. Glassware was routinely oven-dried at 160 ^{o}C for a minimum of 4 h and then connected to a vacuum line before assembling under a dry argon stream. Column chromatography was performed on silica gel 200–425 mesh. THF was distilled from sodium-benzophenone ketyl and DMSO was dried over molecular sieves prior to use. *N*-(*α*-Amidoalkyl) benzotriazoles **1** were prepared according to literature procedures.[12]

General procedure for the preparation of *N*-(*β*-nitroalkyl) amides 4a–l. A mixture of nitroalkane (4 mmol) and potassium *t*-butoxide (0.45 g, 4 mmol) in DMSO (10 mL) was stirred at room temperature for 40 min. To the resulting solution *N*-(*α*-amidoalkyl)benzotriazoles **1** (2 mmol) in DMSO (10 mL) was added dropwise and the mixture was stirred at room temperature for 8 hrs. The mixture was poured into water (40 mL), acidified with acetic acid, and then extracted with ethyl acetate (3x30 mL). The extracts were washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was placed in a silica-gel column and eluted with hexanes/ EtOAc 5:1 to give **4**.

***N*-(2-Nitro-1-*p*-tolylethyl)benzamide (4a).** Colorless microcrystals (79%), mp 147–148 °C. ^{1}H NMR δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.53–7.38 (m, 3H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.23–7.15 (m, 3H), 5.83 (q, *J* = 6.7 Hz, 1H), 4.99 (dd, *J* = 12.9, 6.6 Hz, 1H), 4.78 (dd, *J* = 12.9, 6.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR δ 167.1, 138.7, 133.4, 133.3, 132.0, 129.9, 128.6, 127.0, 126.3, 78.2, 51.4, 21.1. Anal. Calcd. For $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.97; H, 5.72; N, 9.77.

***N*-(2-Methyl-2-nitro-1-*p*-tolylpropyl)benzamide (4b).** Colorless plates (82%), mp 162–163 °C. ^{1}H NMR δ 7.83 (d, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.53–7.43 (m, 3H), 7.12 (s, 4H), 5.48 (d, *J* = 9.7 Hz, 1H), 2.31 (s, 3H), 1.79 (s, 3H), 1.57 (s, 3H). ^{13}C NMR δ 166.5, 138.5, 133.8,

133.1, 131.9, 129.4, 128.7, 127.5, 127.0, 90.5, 59.1, 25.8, 23.5, 21.0. Anal. Calcd. For $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.92; H, 6.44; N, 9.16.

***N*-(2-Methyl-1-nitromethylpropyl)benzamide (4c).** Colorless plates (85%), mp 142–143 °C. ^{1}H NMR δ 7.78 (d, *J* = 7.1 Hz, 2H), 7.56–7.42 (m, 3H), 6.67 (d, *J* = 8.9 Hz, 1H), 4.76 (dd, *J* = 12.9, 5.6 Hz, 1H), 4.63 (dd, *J* = 12.9, 3.8 Hz, 1H), 4.46–4.37 (m, 1H), 2.08–1.96 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR δ 167.3, 133.8, 131.9, 128.7, 127.0, 53.5, 29.9, 19.5, 19.2. Anal. Calcd. For $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.27; H, 6.90; N, 11.85.

***N*-(1-Isopropyl-2-methyl-2-nitropropyl)benzamide (4d).** Colorless needles (87%), mp 125–126 °C. ^{1}H NMR δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.59–7.48 (m, 3H), 7.00 (d, *J* = 10.2 Hz, 1H), 4.45 (dd, *J* = 10.5, 3 .0 Hz, 1H), 2.42–2.17 (m, 1H), 1.74 (s, 3H), 1.65 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR δ 167.6, 133.9, 131.9, 128.8, 126.9, 89.6, 58.9, 28.3, 26.4, 24.0, 22.9, 15.7. Anal. Calcd. For $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.91; H, 7.78; N, 10.79.

***N*-(1-Isopropyl-2-nitrobutyl)benzamide (4e).** Colorless prisms (96%), mp 159–160 °C. ^{1}H NMR δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 6.21 (d, *J* = 9.6 Hz, 1H), 4.67 (dt, *J* = 8.4 , 4.5 Hz, 1H), 4.59–4.51 (m, 1H), 2.22–2.06 (m, 1H), 1.95–1.79 (m, 2H), 1.00 (d, *J* = 6.9 Hz, 6H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR δ 167.7, 133.9, 131.9, 128.7, 126.9, 91.2, 55.6, 28.9, 23.7, 20.2, 16.3, 10.4. Anal. Calcd. For $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.96; H, 7.91; N, 10.62.

***N*-(2-Nitroethyl)benzamide (4f).** Colorless plates (54%), mp 84–85 °C. ^{1}H NMR δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.55–7.40 (m, 3H), 6.93 (br s, 1H), 4.66–4.63 (m, 2H), 4.13–3.98 (m, 2H). ^{13}C NMR δ 168.0, 133.3, 132.0, 128.6, 127.0, 74.5, 37.1. Anal. Calcd. For $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.96; H, 5.12; N, 14.51.

***N*-(2-Methyl-2-nitropropyl)benzamide (4g).** Colorless prisms (86%), mp 121–123 °C. ^{1}H NMR δ 7.76 (d, *J* = 7.1 Hz, 2H), 7.54–7.40 (m, 3H), 6.79 (br s, 1H), 3.95 (d, *J* = 6.6 Hz, 2H), 1.64 (s, 6H). ^{13}C NMR δ 167.8, 133.6, 131.9, 128.6, 126.9, 88.9, 46.4, 24.0. Anal. Calcd. For $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.60; H, 6.42; N, 12.68.

***N*-[2-Methyl-1-(1-nitrocyclohexyl)propyl]benzamide (4h).** Colorless plates (93%), mp 115–116 °C. ^{1}H NMR δ 7.87 (d, J = 7.8 Hz, 2H), 7.56–7.47 (m, 3H), 6.79 (d, *J* = 10.2 Hz, 1H), 4.46 (d, *J* = 10.5 Hz, 1H), 2.65 (d, *J* = 12.6 Hz, 1H), 2.43 (d, *J* = 14.7 Hz, 1H), 2.30–2.21 (m, 1H), 1.86–1.59 (m, 6H), 1.36–1.11 (m, 2H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR δ 167.5, 133.9, 131.9, 128.8, 126.9, 92.3, 58.3, 34.2, 31.8, 27.1, 24.5, 23.4, 22.0, 21.8, 15.1. Anal. Calcd. For $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.27; H, 8.13; N, 9.38.

Decanoic acid (2-nitro-1-*p*-tolylpropyl)amide (4i) [two stereoisomers]. Colorless prisms (89%), mp 79–81 °C. ^{1}H NMR δ 7.14–7.09 (m, 8H), 6.63 (d, *J* = 6.6 Hz, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 5.47–5.39 (m, 2H), 5.02–4.91 (m, 2H), 2.32 (s, 6H), 2.26–2.19 (m, 4H), 1.62 (t, *J* = 6.6 Hz, 4H), 1.52 (dd, *J* = 9.6, 6.9 Hz, 6H), 1.25 (br s, 24H), 0.87 (t, *J* = 6.6 Hz, 6H). ^{13}C NMR δ 172.9, 172.7, 138.7, 138.3, 134.1, 132.7, 129.7, 129.6, 127.0, 126.4, 86.5, 85.3, 55.6, 54.9, 36.7,

31.8, 29.4, 29.3, 29.2, 25.7, 25.6, 22.6, 21.1, 17.2, 15.6, 14.1. Anal. Calcd. For $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 69.26; H, 9.44; N, 7.99.

***N*-[3,3-Dimethyl-1-(1-nitroethyl)butyl]benzamide (4j) [two stereoisomers 1:1].** Colorless prisms (81%), mp 116–117 °C. ^{1}H NMR δ 7.82–7.76 (m, 4H), 7.57–7.42 (m, 6H), 6.63 (d, *J* = 9.6 Hz, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 4.83–4.64 (m, 3H), 4.49 (td, *J* = 9.3, 3.3 Hz, 1H), 1.61–1.51 (m, 9H), 1.35 (dd, *J* = 14.7, 9.9 Hz, 1H), 0.96 (s, 18H). ^{13}C NMR δ 167.1, 166.8, 133.9, 133.8, 131.9, 131.9, 128.8, 128.8, 126.9, 126.9, 87.8, 86.3, 49.6, 48.2, 45.9, 42.0, 30.5, 30.3, 29.5, 29.5 , 29.5, 16.6, 15.6. Anal. Calcd. For $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 65.04; H, 8.11; N, 10.09.

***N*-(2-Nitro-1-thiophen-2-ylbutyl)acetamide (4k) [two stereoisomers].** Colorless microcrystals (58%), mp 113–115 °C. ^{1}H NMR δ 7.28–7.24 (m, 2H), 7.01–6.95 (m, 4H), 6.74 (d, *J* = 8.5 Hz, 1H), 6.36 (d, *J* = 8.5 Hz, 1H), 5.84–5.75 (m, 2H), 4.90–4.80 (m, 2H), 2.11–2.03 (m, 8H), 1.92–1.84 (m, 2H), 1.05–0.97 (m, 6H). ^{13}C NMR δ 169.8, 169.5, 140.3, 138.4, 127.4, 127.2, 126.5, 125.9, 125.4, 125.2, 92.9, 92.4, 50.7, 50.1, 25.1, 23.9, 23.2 (2C), 10.5, 10.4. Anal. Calcd. For $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.89; H, 5.88; N, 11.28.

2,2-Dimethyl-*N*-(2-nitro-1-pyridin-3-ylbutyl)propionamide (4l). Colorless microcrystals (60%), mp 192–193 °C. ^{1}H NMR δ 8.57 (d, *J* = 4.8 Hz, 2H), 7.6 (d, *J* = 7.4 Hz, 1H), 7.32-7.27 (m, 1H), 7.10 (d, *J* = 9.2 Hz , 1H), 5.54 (dd, *J* = 4.5 Hz, 1H), 4.89–4.82 (m, 1H), 2.16-1.82 (m, 2H),1.33 (s, 9H), 1.04 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR δ 178.2, 149.5, 147.9, 133.8, 133.1, 123.7, 93.0, 51.5, 39.0, 27.4, 25.5, 10.3. Anal. Calcd. For $C_{14}H_{21}N_3O_3$: C, 60.20; H, 7.58; N, 15.04. Found: C, 60.47; H, 7.80; N, 15.09.

General procedure for the preparation of *N*-(*β*-cyanoalkyl) amides 6a–g and 7

A mixture of nitrile **5** (2 mmol) and potassium *t*-butoxide (0.25 g, 2.2 mmol) in DMSO (10 mL) was stirred at room temperature for 1h. To the resulting solution of **1** 0.645 g, 2 mmol) in DMSO (10 mL) was added dropwise, and the mixture was stirred at room temperature for 8 hrs. The mixture was quenched with water, and extracted with ethyl acetate (3x30 mL). The extracts were washed with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was placed in a silica-gel column and eluted with hexanes/EtOAc 5:1 to give the pure product.

***N*-[1-(Cyanophenylmethyl)-3,3-dimethylbutyl]benzamide (6a).** Colorless plates (78%), mp 148–150 °C. ^{1}H NMR δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.56–7.33 (m, 8H), 6.75 (d, *J* = 7.5 Hz, 1H), 4.95 (d, *J* = 3.6 Hz, 1H), 4.47–4.40 (m, 1H), 1.69 (dd, *J* = 14.4, 9.9 Hz, 1H), 1.49 (d, *J* = 14.7 Hz, 1H), 0.76 (s, 9H). ^{13}C NMR δ 167.3, 133.6, 132.4, 131.9, 129.0, 128.6, 128.2, 127.7, 127.0, 118.9, 51.6, 43.6, 42.1, 30.1, 29.3. Anal. Calcd. For $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 79.04; H, 7.70; N, 8.85.

***N*-{1-[(4-Bromophenyl)cyanomethyl]-3,3-dimethylbutyl}benzamide (6b).** Colorless plates (87%), mp 155–57 °C. ^{1}H NMR δ 7.82–7.79 (m, 2H), 7.58–7.55 (m, 3H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 7.5 Hz, 1H), 4.56 (d, *J* = 3.9 Hz, 1H), 4.41–4.34 (m, 1H), 1.66 (dd, *J* = 14.7, 10.2 Hz, 1H), 1.43 (d, *J* = 14.4 Hz, 1H), 0.78 (s, 9H). ^{13}C NMR δ 167.3,

133.4, 132.2, 132.1, 131.5, 129.4, 128.8, 127.0, 118.5, 51.5, 43.2, 42.2, 30.1, 29.4. Anal. Calcd. For $C_{21}H_{23}BrN_2O$: C, 63.16; H, 5.81; N, 7.02. Found: C, 63.04; H, 5.83; N, 6.90.

***N*-[1-(Benzo[1,3]dioxol-5-ylcyanomethyl)-3,3-dimethylbutyl]benzamide (6c) [two diastereoisomers isolated].** 1st Diastereoisomer: Colorless prisms (45%), mp 143–144 °C. ^{1}H NMR δ 7.81–7.77 (m, 2H), 7.58–7.42 (m, 3H), 7.02–6.96 (m, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 7.5 Hz, 1H), 6.01 (s, 2H), 4.50 (d, *J* = 3.6 Hz, 1H), 4.40–4.33 (m, 1H), 1.64–1.49 (m, 2H), 0.80 (s, 9H). ^{13}C NMR δ 167.2, 148.2, 147.6, 133.6, 132.1, 128.8, 126.9, 126.0, 121.3, 119.0, 108.6, 108.2, 101.5, 51.6, 43.3, 42.3, 30.2, 29.5. Anal. Calcd. For $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.13; H, 6.64; N, 7.54. 2nd Diastereoisomer: Pale yellow microcrystals (41%), mp 186–188 °C. ^{1}H NMR δ 7.67 (d, *J* = 7.2 Hz, 2H), 7.54–7.48 (m, 1H), 7.45–7.39 (m, 2H), 6.80 (s, 1H), 6.74 (s, 2H), 5.96 (s, 3H), 4.72–4.64 (m, 1H), 4.18 (d, *J* = 4.5 Hz, 1H), 1.78 (d, *J* = 14.4 Hz, 1H), 1.42 (dd, *J* = 14.7, 9.3 Hz, 1H), 0.97 (s, 9H). ^{13}C NMR δ 166.7, 148.1, 147.8, 133.9, 131.8, 128.7, 126.7, 125.4, 122.1, 119.2, 108.4, 103.3, 101.4, 49.8, 45.6, 42.8, 30.5, 29.7. Anal. Calcd. For $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.37; H, 6.73; N, 7.61.

***N*-[2-Cyano-1-(2,2-dimethylpropyl)-2-phenylbutyl]benzamide (6d) [two diastereoisomers isolated].** 1st Diastereoisomer: Colorless prisms (45%), mp 167–168 °C. ^{1}H NMR δ 7.86 (d, *J* = 6.9 Hz, 2H), 7.59–7.33 (m, 8H), 6.41 (d, *J* = 9.6 Hz, 1H), 4.80 (t, *J* = 9.6 Hz, 1H), 2.20–2.12(m, 2H), 1.52 (dd, *J* = 14.7, 10.2 Hz, 1H), 1.64 (d, *J* = 13.8 Hz, 1H), 0.74 (t, *J* = 8.7 Hz, 3H), 0.73 (s, 9H). ^{13}C NMR δ 167.6, 136.3, 133.9, 131,9, 129.0, 128.8, 128.1, 127.0, 126.6, 120.9, 57.1, 53.4, 45.2, 30.5, 30.3, 29.4, 9.6. Anal. Calcd. For $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.38; H, 8.12; N, 8.07. 2nd Diastereoisomer: Colorless microcrystals (41%), mp 153–155 °C. ^{1}H NMR δ 7.55–7.30 (m, 10H), 5.70 (d, *J* = 9.9 Hz, 1H), 4.81 (t, *J* = 9.9 Hz, 1H), 2.31–2.06 (m, 2H), 1.96 (d, *J* = 14.4 Hz, 1H), 1.16 (dd, *J* = 14.4, 9.9 Hz, 1H), 0.95 (t, *J* = 2.4 Hz, 3H), 0.96 (s, 9H). ^{13}C NMR δ 166.5, 134.5, 134.2, 131.5, 129.6, 128.6, 128.2, 127.3, 126.5, 121.4, 55.4, 52.2, 46.6, 30.6, 29.6, 29.3, 9.7. Anal. Calcd. For $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.55; H, 8.23; N, 8.06.

***N*-(2-Cyano-1-naphthalen-1-yl-2-phenylbutyl)benzamide (6e) [two diastereoisomers isolated].** 1st Diastereoisomer: Colorless prisms (41%), mp 104–105 °C. ^{1}H NMR δ 8.51 (d, *J* = 8.4 Hz, 1H), 7.92–7.83 (m, 3H), 7.73–7.64 (m, 3H), 7.57–7.24 (m, 10H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.76 (d, *J* = 9.6 Hz, 1H), 2.09 (sextet, *J* = 6.9 Hz, 1H), 1.59 (sextet, *J* = 7.5 Hz, 1H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR δ 166.2, 135.9, 134.1, 133.7, 133.6, 132.0, 131.6, 130.7, 129.2, 129.1, 129.0, 128.5, 127.2, 127.0, 126.8, 126.0, 125.3, 124.5, 122.8, 120.6, 56.6, 53.2, 30.1, 9.5. Anal. Calcd. For $C_{28}H_{24}N_2O$: N, 6.93. Found: N, 6.74. 2nd Diastereoisomer: Colorless plates (32%), mp 214–216 °C. ^{1}H NMR δ 8.21 (d, *J* = 8.21 Hz, 1H), 7.83 (dd, *J* = 13.2, 7.2 Hz, 3H), 7.68 (dd, *J* = 14.7, 8.1 Hz, 2H), 7.52–7.28 (m, 8H), 7.11–7.01 (m, 3H), 6.90 (d, *J* = 9.9 Hz, 1H), 6.93 (d, *J* = 9.6 Hz, 1H), 2.53 (sextet, *J* = 7.5 Hz, 1H), 2.38 (sextet, *J* = 7.2 Hz, 1H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR δ 167.2, 135.0, 133.7, 133.6, 133.5, 132.0, 131.4, 128.8, 128.7, 128.6, 127.7, 127.1, 126.7, 126.6, 125.8, 124.9, 124.7, 122.9, 121.9, 55.6, 53.1, 32.8, 9.4. Anal. Calcd. For $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 82.96; H, 6.02; N, 6.96.

***N*-(2-Cyano-2-phenylethyl)benzamide (6f).** Colorless plates (58%), mp 120–122 °C. ^{1}H NMR δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.53–7.35 (m, 8H), 7.12 (t, *J* = 5.7 Hz, 1H), 4.37 (dd, *J* = 9.3, 6.3 Hz, 1H), 3.98–3.90 (m, 1H), 3.67–3.57 (m, 1H). ^{13}C NMR δ 168.1, 133.4, 132.8, 131.9, 129.2, 128.6, 127.5, 127.0, 119.8, 44.7, 37.7. Anal. Calcd. For $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.38; H, 5.69; N, 11.05.

***N*-[2-Cyano-2-(2,4-dichloro-phenyl)ethyl]benzamide (6g).** Colorless prisms (65%), mp 136–137 °C. ^{1}H NMR δ 7.76 (d, *J* = 7.3 Hz, 2H), 7.56–7.41 (m, 5H), 7.31 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.77 (t, *J* = 6.9 Hz, 1H), 4.79 (dd, *J* = 8.4, 5.7 Hz, 1H), 4.06–3.97 (m, 1H), 3.76–3.67 (m, 1H). ^{13}C NMR δ 167.9, 135.6, 134.1, 133.3, 132.1, 130.2(2C), 129.2, 128.7, 128.1, 127.0, 118.7, 42.3, 35.2. Anal. Calcd. For $C_{16}H_{12}Cl_2N_2O$: C, 60.21; H, 3.69; N, 8.79. Found: C, 60.11; H, 3.70; N, 8.50.

***N*-(2-Cyano-2-phenylbutyl)benzamide (6h).** Colorless prisms (61%), mp 110–111 °C. ^{1}H NMR δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.51–7.32 (m, 8H), 6.56 (br s, 1H), 4.21 (dd, *J* = 13.5, 7.2 Hz, 1H), 3.75 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.21–2.01 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR δ 167.6,135.6, 133.7, 131.7, 129.1, 128.5, 128.3, 126.9, 126.2, 121.3, 507, 47.4, 30.2, 9.3. Anal. Calcd. For $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.48; H, 6.62; N, 9.87.

***N*-[2-Cyano-2-(2,4-dichlorophenyl)-bis-(1-naphthalen-1-yl-ethyl]benzamide (7).** Colorless microcrystals (44%), mp 211–213 °C. ^{1}H NMR δ 8.30 (d, *J* = 8.1 Hz, 1H), 7.98–7.67 (m, 9H), 7.59–7.35 (m, 12H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.20 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.95–6.80 (m, 3H), 6.69–6.58 (m, 2H), 5.54 (d, *J* = 6.9 Hz, 1H), 5.03 (d, *J* = 3.9 Hz, 1H). ^{13}C NMR δ 167.2, 166.7, 135.6, 135.2, 134.1, 133.9, 33.8, 133.6, 133.5, 133.4, 133.3, 132.3, 132.1, 132.0, 131.3, 131.1, 130.5, 130.0, 129.8, 129.7, 129.5, 129.3, 129.1, 129.7, 128.5, 127.7, 127.3, 127.0, 126.9, 126.4, 126.2, 125.0, 123.7, 122.6, 121.9, 118.4, 118.3., 49.7, 41.2, 40.0. Anal. Calcd. For $C_{44}H_{31}Cl_2N_3O_2$: N, 5.96. Found: N, 6.21.

General procedure for the preparation of *N*-acylpropargylamines 11a–g

Method A. To a solution of alkyne **9** (2 mmol) in dry THF (10 mL), *n*-BuLi (2.6 mL, 1.6 M in pentane, 4.2 mmol) was added at -78 ^{o}C. The solution was stirred at -78 ^{o}C for 1 h, and a solution of **1** (2 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 10 h while the temperature was allowed to rise to 20 ^{o}C. After quenching with water (20 mL) and extraction with EtOAc (3x25 mL), the combined organic layers were washed with water, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulted oil was subjected to column chromatography (eluent: ethyl acetate/ hexanes = 1: 10 then 1: 5) to give the pure product.

Method B. To a solution of ethylmagnesium bromide (5 mmol) (prepared *in situ*) in THF (10 mL), alkyne **9** (2.7 mmol) was added. The contents were heated under reflux until evolution of ethane was ceased then left to attain room temperature. A solution of **1** (1.5 mmol) in THF (10 mL) was added dropwise to Grignard solution and mixture was stirred for 1h. After quenching with water (20 mL) and extraction with EtOAc(4x25 mL), the combined organic layers were dried over $MgSO_4$ and solvent removed in vacuo. The resulted oil was subjected to column chromatography (eluent: hexanes/EtOAc = 5:1) to give the pure product.

***N*-(3,3-Dimethyl-1-phenylethynylbutyl)benzamide (11a).** Colorless prisms (53%), mp 118–120 °C. ^{1}H NMR δ 7.80 (d, *J* = 6.9 Hz, 2H), 7.52–7.40 (m, 4H), 7.31–7.29 (m, 2H), 6.33 (d, *J* = 8.1 Hz, 1H), 5.30–5.23 (m, 1H), 1.92–1.78 (m, 2H), 1.09 (s, 9H). ^{13}C NMR δ 165.9, 134.1, 131.5(2C), 128.4, 128.1(2C), 127.0, 22.7, 90.1, 82.9, 49.9, 39.6, 30.4, 29.7. Anal. Calcd. For $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.48; H, 7.87; N, 4.68.

***N*-(4-Methyl-2-phenylethynylpentyl)benzamide (11b).** Colorless prisms (63%), mp 95–96 °C. ^{1}H NMR δ 7.81 (d, *J* = 7.3 Hz, 2H), 7.53–7.41 (m, 5H), 7.31–7.27 (m, 3H), 6.36 (d, *J* = 8.2 Hz, 1H), 5.26 (q, *J* = 8.0 Hz, 1H), 1.94–1.88 (m, 1H), 1.75 (t, *J* = 7.1 Hz, 2H), 1.02 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR δ 166.3, 134.2, 131.8, 131.7, 128.6, 128.4, 128.3, 127.0, 122.7, 88.7, 83.2, 45.4, 41.0, 25.4, 23.0, 22.1. Anal. Calcd. For $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.24; H, 7.58; N, 4.89.

N-(3-Methyl-1-*p*-tolylethynylbutyl)benzamide (11c). Colorless microcrystals (86%), mp 112–113 °C. ^{1}H NMR δ 7.86 (d, *J* = 7.0 Hz, 2H), 7.58–7.62 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.3 (q, *J* = 8.0 Hz, 1H), 2.39 (s, 3H), 2.00–1.93 (m, 1H), 1.82–1.75 (m, 2H), 1.08 (d, *J* = 1.1 Hz, 3H), 1.06 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR δ 166.2, 138.4, 134.2, 131.6 (2C), 129.0, 128.5, 127.0, 119.5, 87.9, 83.2, 45.4, 41.0, 25.3, 22.9, 22.0, 21.4. Anal. Calcd. For $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.31; H, 7.80; N, 4.56

***N*-(1-Isopropyl-3-*p*-tolylprop-2-ynyl)benzamide (11d).** Colorless microcrystals (85%), mp 128–129 °C. ^{1}H NMR δ 7.80 (d, *J* = 7.0 Hz, 2H), 7.52–7.43 (m, 3H), 7.33 (d, *J* = 8.0 Hz , 2H), 7.11 (d, *J* = 8 .0 Hz, 2H) 6.38 (d, *J* = 8.6 Hz , 1H), 5.1 (dd, *J* = 8.4, 5.4 Hz, 1H), 2.35 (s, 3H), 2.20–2.09 (m, 1H), 1.56 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR δ 166.5, 139.4, 138.5, 131.7, 129.1, 128.7, 127.0, 122.1, 119.58, 86.2, 84.3, 48.3, 33.3, 21.5, 19.1, 17.8. Anal. Calcd. For $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.54; H, 7.49; N, 4.73.

***N*-(1-Isobutyloct-2-ynyl)benzamide (11e).** Colorless oil (80%).^{1}H NMR δ 7.78, (d, *J* = 6.0 Hz, 2H), 7.65–7.40 (m, 3H), 6.20 (d, *J* = 8.5 Hz , 1H), 4.90 (q, *J* = 5.4, 3.2 Hz, 1H), 2.23 (dt, *J* = 7.0, 2.0 Hz, 2H), 1.86–1.78 (m, 1H), 1.56 (t, *J* = 7.1 Hz, 2H), 1.58–1.26 (m, 7H), 0.98 (d, *J* = 6.6 Hz, 6H), 0.9 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR δ 166.1, 134.3, 131.5, 128.5, 126.9, 83.7, 76.4, 45.6, 40.8, 31.0, 28.3, 25.3, 22.9, 22.1, 18.6, 14.0. Anal. Calcd. For $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, C, 80.15; H, 9.96; N, 4.83.

***N*-(1-Thiophen-2-yl-non-2-ynyl)acetamide (11f).** Colorless microcrystals (41%), mp 61–62 °C. ^{1}H NMR δ 7.21 (dd, *J* = 5.0, 4.1 Hz, 1H), 7.13 (d, *J* = 3.4 Hz, 1H), 6.93 (dd, *J* = 3.6, 1.5 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 1H), 2.23 (dt, *J* = 7.0, 2.0 Hz, 2H), 1.99 (s, 3H), 1.56–1.51 (m, 2H), 1.42–129 (m, 6H), 0.89(t, *J* = 6.7 Hz, 3H). ^{13}C NMR δ 168.6, 143.7 126.6, 125.5, 125.1, 84.9, 77.4, 40.5, 31.2, 28.4, 28.3, 23.0, 22.4, 18.6, 14.0. Anal. Calcd. For $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; N, 5.32. Found: C, 68.47; H, 8.20; N, 5.50.

2,2-Dimethyl-*N*-(3-phenyl-1-pyridin-3-yl-prop-2-ynyl)propionamide (11g). Colorless microcrystals (41%), mp 151–152 °C. ^{1}H NMR δ 8.69 (d, *J* = 2.0 Hz, 1H), 8.64 (d, *J* = 8.2 Hz, 1H), 8.52 (d, *J* = 6.2 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.50–7.40 (m, 6H), 6.21 (d, *J* = 8.2 Hz, 1H), 1.14 (s, 9H). ^{13}C NMR δ 176.8, 148.7,148.1, 135.6, 134.4, 131.5, 128.9, 128.7, 123.6,

121.9, 87.9, 83.8, 42.2, 40.3, 38.1, 27.2. Anal. Calcd. For $C_{19}H_{20}N_2O$: C, 6 78.05; H, 6.89; N, 9.58. Found: C, 6 78.14; H, 7.13; N, 9.55.

General procedure for the preparation of esters of *β-N*-acylamino acids 13

Method A. To a solution of ester **12 (**2 mmol) in dry THF (10 mL), *n*-BuLi (2.6 mL, 1.6 M in pentane, 4.2 mmol) was added at -78 ^oC. The solution was stirred at -78 ^oC for 1 h, and a solution of **1** (0.504 g, 2 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 10 h while the temperature was allowed to rise to 20 ^oC. After quenching with water (20 mL) and extraction with EtOAc (3x25 mL), the combined organic layers were washed with water (25 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting oil was subjected to column chromatography (eluent: ethyl acetate/ hexanes = 1: 10 then 1: 5) to give the pure product.

Method B. To a solution of **12** (6 mmol), in dry DMSO (10 mL), *t*-BuOK (0.67g, 6 mmol) was added at 25 ^oC. The solution was stirred at room temperature for 1 h, and a solution of **1** (3 mmol) in DMSO (10 ml) was added. The mixture was stirred for 12 h, quenched with water (20 mL) and extracted with EtOAc(4x25 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and solvent was removed *in vacuo* and the resulting oil was subject to column chromatography (eluent: hexanes/ethyacetate = 5:1) to give the pure product.

3-Benzoylamino-5,5-dimethyl-2-phenylhexanoic acid methyl ester (13a). Colorless prisms (68%), mp 183–185 °C. ^{1}H NMR δ 7.58 (d, *J* = 6.9 Hz, 2H), 7.48–7.28 (m, 8H), 6.16 (d, *J* = 9.2 Hz, 1H), 4.70–4.62 (m, 1H), 4.09 (d, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 1.71–1.52 (m, 2H), 0.83 (s, 9H). ^{13}C NMR δ 172.9, 166.6, 154.5, 136.0, 134.9, 131.3, 129.0, 128.5, 127.5, 126.6, 56.9, 52.0, 49.8, 45.2, 30.6, 29.4. Anal. Calcd. For $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.88; H, 8.01; N, 3.91.

3-Benzoylamino-5-methyl-2-naphthalen-1-ylhexanoic acid methyl ester (13b). Colorless microcrystals (92%), mp 161–162 °C. ^{1}H NMR δ 8.53 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 3.7, 2.5 Hz, 1H), 7.75–7.72 (m, 1H), 7.60–7.39 (m, 8H), 6.40 (d, *J* = 8.5 Hz, 1H), 5.10 (d, *J* = 6.3 Hz, 1H), 4.96–4.87 (m, 1H), 3.75 (s, 3H), 2.20–1.95 (m, 1H), 1.66–1.60 (m, 1H), 1.45–1.32 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR δ 173.7, 167.2, 134.5, 133.9, 132.2, 131.4, 131.8, 128.9, 128.5, 128.3, 127.0, 126.8, 126.1, 125.9, 125.1, 123.2, 52.0, 51.1, 49.6, 39.9, 25.3, 23.6, 21.1. Anal. Calcd. For $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.77; H, 6.76; N, 3.57.

3-Benzoylamino-4-methyl-2-naphthalen-1-yl-pentanoic acid methyl ester (13c) (two diastereoisomers 1:3). Colorless microcrystals (89%), mp 150–152 °C. ^{1}H NMR δ 8.23 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.85 (dd, *J* = 8.1, 8.0 Hz 3H), 7.79 (d, *J* = 7.3 Hz, 2H), 6.97 (d, *J* = 7.5 Hz, 3H), 5.59 (d, *J* = 10.6 Hz, 1H), 5.21 (d t, *J* = 10.6, 3.2 Hz, 1H), 5.00 (d, *J* = 3.6 Hz, 1H), 4.78 (d, *J* = 10. 7 Hz, 1H), 4.08–3.85 (m, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 2.15–2.08 (m, 2H), 1.23 (d, *J* = 6.73 Hz, 1H), 1.1 (d, *J* = 6.9 Hz, 4H), 1.08 (d, *J* = 2.9 Hz, 4H), 1.03 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR δ 174.4, 172.6, 167.6, 166.7, 134.8, 134.1, 133.9, 132.0, 131.8, 131.7, 131.2, 130.9, 129.3, 128.5, 128.2, 126.8, 126.7, 126.3, 126.1, 125.9, 125.7, 125.5, 125.0, 124.9,

122.3, 122.1, 57.0, 55.2, 52.3, 51.8, 48.6, 46.5, 32.4, 31.2, 20.7, 20.2, 19.3, 16.1. Anal. Calcd. For $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.47; H, 7.06; N, 3.81.

3-Acetylamino-2-phenyl-3-thiophen-2-yl-propionic acid methyl ester (13d). Colorless microcrystals (75%), mp 166–168 °C. ^{1}H NMR δ 7.33–7.30 (m, 5H), 7.18–7.12 (m, 2H), 6.90 (d, *J* = 3.6 Hz, 2H), 5.78 (dd, *J* = 9.5, 5.4 Hz, 1H), 4.2 (d, *J* = 5.3 Hz, 1H), 3.68 (s, 3H), 1.95 (s, 3H). ^{13}C NMR δ 173, 169.2, 144.1, 134.9, 128.7, 128.1, 128.0, 126.8, 124.5, 124.4, 56.0, 52.3, 51.6, 23.2. Anal. Calcd. For $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 62.99; H, 5.66; N, 4.51.

2-Benzoyl-3-benzoylamino-5,5-dimethylhexanoic acid ethyl ester (13e). Colorless plates (84%), mp 131–132 °C. ^{1}H NMR δ 8.11–8.08 (m, 2H), 7.79–7.76 (m, 2H), 7.62–7.41 (m, 6H),7.11 (d, *J* = 9.0 Hz, 1H), 4.92 (ddt, *J* = 9.6, 3.4, 2.1 Hz, 1H), 4.80 (d, *J* = 3.6 Hz, 1H), 4.34–4.06 (m, 2H), 1.89 (dd, *J* = 15.0, 9.6 Hz, 1H), 1.52 (dd, *J* = 14.7, 1.8 Hz, 1H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H). ^{13}C NMR δ 195.5, 168.8, 166.5, 136.0, 134.4, 134.0, 131.5, 129.0, 128.6, 128.5, 126.9, 61.6, 58.1, 47.2, 46.0, 30.6, 29.4, 13.9. Anal. Calcd. For $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 73.07; H, 7.54; N, 3.77.

2-(Benzoylamino-*p*-tolylmethyl)-3-oxobutyric acid methyl ester (13f). Colorless prisms (88%), mp 193–194 °C. ^{1}H NMR δ 7.86–7.79 (m, 2H), 7.51–7.40 (m, 3H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 5.92 (dd, *J* = 8.9, 5.2 Hz, 1H), 4.21 (d, *J* = 5.1 Hz, 1H), 3.71 (s, 3H), 2.30 (s, 3H), 2.18 (s, 3H). ^{13}C NMR δ 204.5, 167.8, 166.7, 137.5, 136.1, 134.1, 131.6, 129.4, 128.6, 127.1, 126.2, 62.0, 52.9, 52.6, 31.4, 21.0. Anal. Calcd. For $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 71.08; H, 6.31; N, 4.43.

2-(Benzoylaminonaphthalen-1-ylmethyl)-3-oxobutyric acid benzyl ester (13g) (two diastereoisomers). Colorless microcrystals (96%), mp 122–123 °C. ^{1}H NMR δ 8.45 (d, *J* = 8.7 Hz, 1H), 8.26-8.16 (m, 3H), 7.91–7.75 (m, 8H), 7.65–7.34 (m, 14H), 7.31–7.25 (m, 8H), 7.06–7.04 (m, 2H), 6.88 (dd, *J* = 9, 3.6 Hz, 1H), 6.80 (dd, *J* = 8.4, 4.2 Hz, 1H), 5.18 (s, 2H), 5.05 (s, 2H), 4.41 (d, *J* = 6.0 Hz, 1H), 4.31 (d, *J* = 3.0 Hz, 1H), 2.48 (s, 3H), 2.00 (s, 3H). ^{13}C NMR δ 204.9, 200.9, 169.4, 167.3, 166.5, 166.4, 134.8, 134.5, 134.4, 134.1, 133.9, 133.6, 131.8, 131.6, 130.1, 129.9, 129.3, 129.2, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.1, 127.0, 127.0, 125.9, 125.2, 123.9, 123.7, 122.4, 121.9, 67.8, 67.3, 63.0, 60.5, 49.4, 48.1, 31.9, 28.8. Anal. Calcd. For $C_{29}H_{25}NO_4$: C, 77.14; H, 5.58; N, 3.10. Found: C, 76.82; H, 5.43; N, 3.07.

References

1. Zaugg, H. E. *Synthesis* **1970**, 49.
2. (a) Zaugg, H. E. *Synthesis* **1984**, 49. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (c) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1047. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

3. (a) Marson, C. M. *Arkivoc* **2001**, (*i*), 1. (b) Gonzalez-Temprano, I.; Sotomayor, N. J; Lete, E. *Synlett* **2002**, 593. (c) Osante, I.; Lete, E.; Sotomayor, N. *Tetrahedron Lett*. **2004**, *45*, 1253.
4. (a) Bogolyubov, A. A.; Chernysheva, N. B.; Nesterov, V. V.; Antipin, M. Y.; Semenov, V. V. *Arkivoc* **2000**, (*i*), 497. (b) Jung, J.-W.; Shin, D.-Y.; Seo, S.-Y.; Kim, S.-H.; Paek, S.-M.; Jung, J.-K.; Suh, Y.-G.; *Tetrahedron Lett*. **2005**, *46*, 573.
5. (a) Venkov, A. P.; Likanov, L. K.; Mollov, N. M. *Synthesis* **1982**, 486. (b) Ardeo, A.; Garcia, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron Lett*. **2003**, *44*, 8445. (c) Gonzalez-Temprano, I.; Osante, I.; Lete, E.; Sotomayor, N. *J. Org. Chem*. **2004**, *69*, 3875.
6. Katritzky, A. R.;. Drewniak, M.; Lue, P.; *J. Org. Chem.* **1988**, *53*, 5854.
7. Katritzky, A. R.; Pernak, J.; Fan, W. Q.; Saczewski, F. *J. Org. Chem.* **1991**, *56*, 4439.
8. Katritzky, A. R.; Shobana, N.; Harris, P. A. *Org. Prep. Proceed. Int.* **1992**, 121.
9. (a) Katritzky, A. R.; Takahashi, I.; Fan, W. Q.; Pernak, J. *Synthesis* **1991**, 1147. (b) Katritzky, A. R.; Fan, W. Q.; Black, M.; Pernak, J. *J. Org. Chem.* **1992**, *57*, 547.
10. Katritzky, A. R.; Pernak, J.; Fan, W. Q. *Synthesis* **1991**, 868.
11. Katritzky, A. R.; Urogdi, L.; Mayence, A. *J. Org. Chem.* **1990**, *55*, 2206.
12. Katritzky, A. R.; Drewniak, M. *J. Chem. Soc., Perkin Trans 1* **1988**, 2339.
13. Krawczyk, H.; Wolf, W. M. Sliwinski, M. *J. Chem. Soc., Perkin Trans 1* **2002**, 2794.
14. Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett*. **2002**, *4*, 2621.
15. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B*, 4th Edn.; New York: Kluwer Academic/Plenum Pub., 2000; p 100.
16. Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549.
17. Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.
18. Hui, X.; Desrivot, J.; Bories, C.; Loiseau, P. M.; Franck, X.; Hocquemiller, R.; Figadere, B. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 815.
19. Gissot, A.; N'Gouela, S.; Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem*. **2004**, *69*, 8997.
20. Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2005**, *44*, 612.
21. Katritzky, A. R.; Saczewski, F. *Gazzetta Chimica Italiana* **1990**, *120,* 375.
22. (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (b) Ballini, R.; Petrini, M. *Tetrahedron Lett*. **1999**, *40*, 4449.
23. Reddy, M. V. R.; Mehrotra, B.; Vankar, Y. D. *Tetrahedron Lett*. **1995**, *36*, 4861.
24. Easton, C. J.; Roselt, P. D.; Tiekink, E. R. T. *Tetrahedron* **1995**, *51*, 7809.
25. Hodgson, D. R. W.; Sanderson, J. M. *Chem. Soc. Rev*. **2004**, *33*, 422.
26. (a) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657. (b) Fondekar, K. P. P.; Volk, F.-J.; Khaliq-uz-Zaman, S. M.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2002**, *13*, 2241.
27. Kita, Y.; Shibata, N.; Kawano, N.; Yoshida, N.; Matsumoto, K.; Takebe, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2321.
28. Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem*. **2000**, *65*, 1344.

29. Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.; Kobayashi, J. *J. Am. Chem. Soc.* **2002**, *124*, 13678.
30. Katritzky, A. R.; Abdel-Fattah, A. A. A.; Vakulenko, A. V.; Tao, H. *J. Org. Chem*. **2005**, *70*, 9191.
31. Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem*. **2003**, *68*, 4932.
32. Katritzky, A. R.; Abdel-Fattah, A. A. A.; Steel, P. J. *Tetrahedron Lett.* **2006***, 47,* 1465
33. Carlier, P. R.; Lo, K. M.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem*. **1995**, *60*, 7511.
34. Cossy, J.; Schmitt, A.; Cinquin, C.; Buisson, D.; Belotti, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1699.
35. (a) Yu, P. H.; Davis, B. A.; Boulton, A. A. *J. Med. Chem*. **1992**, *35*, 3705. (b) Shirota, F. N.; DeMaster, E. G.; Nagasawa, H. T. *J. Med. Chem*. **1979**, *22*, 463.
36. Stütz, A. *Angew. Chem. Int. Ed*. **1987**, *26*, 320.
37. Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem*. **1995**, *60*, 1590.
38. (a) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Molecular Diversity* **2003**, *7*, 135. (b) Wei, C.; Li, C.-J. *J. Am. Chem*. *Soc*. **2003**, *125*, 9585. (c) Wei, C.; Li, Z.; Li, C-J. *Org. Lett*. **2003**, *5*, 4473. (d) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett*. **2004**, *6*, 1001.
39. Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2535.
40. Mahrwald, R.; Quint, S. *Tetrahedron Lett*. **2001**, *42*, 1655.
41. Fishcher, C.; Carreira, E. M. *Org. Lett*. **2001**, *3*, 4319.
42. Katritzky, A. R.; Gallos, J. K.; Yannakopoulou, K. *Synthesis* **1989**, 31.
43. Ahn, J. H.; Joung, M. J.; Yoon, N. M. *J. Org. Chem*. **1999**, *64*, 488.
44. Mukerjee, A. K.; Srivastava, R. C. *Synthesis* **1973,** 327**.**
45. (a) Tang, W; Zhang, X. *Org. lett*. **2002**, *4*, 4159. (b) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952. (c) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, III, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.
46. (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.
47. Kobayashi, S.; Ishitani, H.; Komiyama, S.; Oniciu, D. C.; Katritzky, A. R. *Tetrahedron Lett*. **1996**, *37*, 3731.
48. Katritzky, A. R.; Shobana, N.; Harris, P. A. *Tetrahedron Lett*. **1990**, *31*, 3999.