New and simple synthesis of acid azides, ureas and carbamates from carboxylic acids: application of peptide coupling agents EDC and HBTU†

Vommina V. Sureshbabu,* H. S. Lalithamba, N. Narendra and H. P. Hemantha

Received 29th September 2009, Accepted 6th November 2009
First published as an Advance Article on the web 8th December 2009
DOI: 10.1039/b920290k

Conversion of carboxylic acids into acid azides using peptide coupling agents, EDC and HBTU is described. The procedure is efficient, practical and applicable to a diverse range of carboxylic acids including *N*-protected amino acids. Using the same reagents, one-pot synthesis of ureas, dipeptidyl urea esters and carbamates from acids has also been achieved.

Acyl azides, in general, and *N*-protected α-amino acid azides in particular, have occupied a place of their own importance in organic[1] and peptide as well as peptidomimetic[2] syntheses. They are extensively used in the preparation of amides and peptides, and a wide range of other compounds such as nitriles, and several classes of heterocycles.[1,3] The Curtius rearrangement of acyl azides into isocyanates is of paramount value in synthetic chemistry. It is widely used in the preparation of amines, ureas and carbamates. A number of natural products and pharmacologically important compounds containing uriedo linkages,[4] ureidopeptidomimetics,[5] partially modified retro-inverso (PMRI) peptides, formamides and unnatural amino acids have been prepared *via* this rearrangement.[2,6] Due to such vast utility of acid azides, the development of efficient routes for their synthesis is important.

The two well known routes for the preparation of acid azides are the reaction of NaN_3 with an acid chloride[7] or mixed anhydride.[8] The acid chloride method offers disadvantages at the preparation of acid chloride itself. These include prolonged reaction duration, incompatibility with acid cleavable groups, and storage and stability problems associated with moisture sensitive acid chlorides. Also the poor solubility of NaN_3 in organic reaction medium requires the usage of a phase transfer catalyst,[9] or catalysts such as ZnI_2[10] to improve the yield of acid azides. Alternately, protocols for the *in situ* generation of acid chlorides using $SOCl_2$/DMF–NaN_3,[11] cyanuric chloride/*N*-methylmorpholine,[12] triphosgene/triethylamine,[13] *N*,*N*-chloromethylenedimethylammonium chloride,[14] followed by coupling with an azide have also been reported. But these methods are not suitable for acids such as *N*-Boc/Z-α-amino acids whose acid chlorides are unstable. Preparation of acid azides *via* mixed anhydrides has been used to advantage. Yet, this method uses chloroformates which are inconvenient for handling. Katritzky *et al.*, recently prepared acid azides from acids in a two step route involving *N*-acyl benzotriazoles as stable and reactive intermediates.[15] Acid azides, such as Boc/Z-amino acid azides, have also been prepared through a multi-step route starting from acids by hydrazinolysis of the methyl/ethyl esters followed by reaction of the resultant hydrazide with nitrosyl donors like HNO_2.[6a,b,16] A few other reported protocols involve treatment of acids with diphenylphosphoryl azide (DPPA) or Deoxo-Fluor/NaN_3[17] and that of aldehydes with Dess–Martin reagent/NaN_3.[18] But most of these methods either involve lengthy procedures or expensive reagents (*e.g.*, DPPA) or are less commonly used.

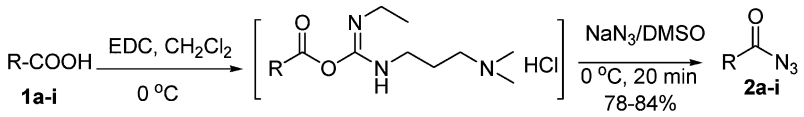
Peptide coupling agents, starting from carbodiimides[19] to uronium reagents such as 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HATU)[19a,20] are versatile reagents for activation of the carboxylic group. They have enabled the execution of an acid–amine coupling in a single step without the requirement for pre-activation of the acids. Their main advantages include a practically convenient procedure, rapid *in situ* activation, minimal side reactions, commercial availability, stability, solubility in a wide range of solvents including water and easy removal of the byproducts of coupling.[21] Their high practical utility is also marked by the availability of a plethora of reagents for applications in a diverse range of conditions which has resulted in their successful application in organic synthesis including natural products synthesis.[22] In the case of carbodiimide mediated couplings, the use of additives 1-hydroxybenzotriazole (HOBt),[23] 1-hydroxy-7-azabenzotriazole (HOAt),[20] *N*-hydroxysuccinimide,[24] and 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine[25] significantly improves the yield and also suppresses epimerization when α-amido acids are activated.

In view of these advantages, we envisaged employing peptide coupling agents for the first time for the general synthesis of acyl azides. This paper describes the direct conversion of a diverse range of carboxylic acids including Fmoc/Z-α-amino acid into acyl azides using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3,-tetramethyluroniumhexafluorophosphate (HBTU). In addition, application of these reagents in the one pot synthesis of ureas, ureidopeptides and carbamates is also presented.

Our initial objective was to convert acids into acid azides using carbodiimides. For this purpose, to a solution of pyridine 3-carboxylic acid **1a** in dry CH_2Cl_2 at 0 °C was added EDC and then NaN_3 in DMSO (or in CH_3CN with a drop of water). The *O*-acylisourea generated readily reacted with NaN_3 leading to the

Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr. B. R. Ambedkar Veedhi, Bangalore – 560 001, India. E-mail: sureshbabuvommina@rediffmail.com, haricch@hotmail.com

† Electronic supplementary information (ESI) available: Spectral characterization data for all the compounds and copies of mass and NMR spectra; references for the known ureas and carbamates. See DOI: 10.1039/b920290k



1a : pyridine-3-carboxylic acid; **1b** : pyridine-2-carboxylic acid; **1c** :furan-2-carboxylic acid; **1d** : thiophene-2-carboxylic acid; **1e**: 2-(1 *H* indol-3yl) acetic acid; **1f**: cinnamic acid; **1g**: phenyl acetic acid; **1h**: *p*-nitro benzoic acid; **1i**: *p*-(Fmoc-amino) benzoic acid

Scheme 1 Synthesis of acid azides **2**.

Table 1 Reagents and conditions for the preparation of **2a**

Entry	Reagent	Base/additive	Solvent	Time/min	Yield (%)
1	EDC	—	CH_2Cl_2	20	80
2	EDC	HOBt (1.1 eq)	CH_2Cl_2	20	83
3	EDC	HOAt (1.1 eq)	CH_2Cl_2	15	85
4	DCC	—	THF	25	79
5	DCI	—	THF	25	76
6	PyBOP	DIPEA	THF	30	73
7	HATU	DIPEA	THF	05	84
8	$(Boc)_2O$	DIPEA	THF	25	77

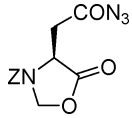
formation of the corresponding acid azide **2a** (Scheme 1). The reaction was completed in 20 min (TLC). A simple work-up led to the isolation of **2a** in 83% yield, which was initially characterized by the IR (strong peak at 2135 cm^{-1} corresponding to the azido group) and then confirmed through mass and NMR analysis.

Encouraged by the result, the usefulness of other popular coupling agents for the preparation of acid azides from acids was studied. Boc-anhydride,[26] a reagent originally introduced for the preparation of *tert*-butyl carbamates from amines, has also been used as carboxylic activator in reactions such as the macrolactonization of ω-hydroxy acids[27] and in peptide coupling for the preparation of dipeptides.[28] Further, the Boc_2O/NaN_3 system has been used for the *in situ* generation of acid azides that have been converted into carbamates without isolation.[29] In the present study, treatment of **1a** with Boc_2O and NaN_3 resulted in the acid azide **2a** which was isolated in 77% yield. The other widely used coupling agent HATU was also studied. A comparative study of the preparation of **2a** employing different coupling agents is summarized in Table 1. Carbodiimides resulted in higher yields of **2a** and EDC was especially useful due to the easy removal of the water soluble urea byproduct. Although HATU could provide an increased yield, its extensive application was limited by its significantly higher cost than EDC. Hence EDC was further used to prepare a series of diversely functionalized acyl azides **2a–i** (Table 2) in 78–84% yield.

Table 2 List of acid azides prepared *via* Scheme 1

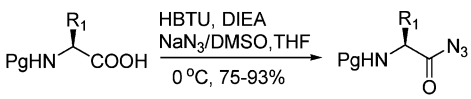
Compd.	R-CON_3	Yield (%)	Ref.	M.p./°C
2a	pyridine-3-carboxylic acid azide	83	15	gum
2b	pyridine-2-carboxylic acid azide	80	15	gum
2c	furan-2-carboxylic acid azide	84	15	64
2d	thiophene-2-carboxylic acid	79	15	35
2e	2-(1*H*-indol-3yl)acetyl azide	80	—	gum
2f	cinnamoyl azide	78	13	83
2g	phenylacetyl azide	83	13	88
2h	*p*-nitrobenzoyl azide	82	13	68
2i	*p*-(Fmoc-amino)benzoyl azide	79	—	gum

Table 3 List of *N*-Fmoc/Z-amino acid azides prepared *via* Scheme 2

Compd.[2c]	R^1	Yield (%)	M.p./°C	HRMS: Found/ Calcd. $(M + Na)^+$
4a	CH_3	82	163	359.1126/359.1120
4b	$CH(CH_3)_2$	81	169	387.1423/387.1433
4c	$CH_2CH(CH_3)_2$	85	122	401.1573/401.1590
4d	$CH(CH_3)CH_2CH_3$	78 (70[a])	152	401.1596/401.1590
4e	$CH_2C_6H_5$	82 (80[c])	175	451.1615/451.1172[b]
4f	-$(CH_2)_3$-[proline]	81	74	385.1133/385.1277
4g	$CH_2C_6H_5$	85	146	347.1098/347.1120
4h		80	*gum*	327.1/327.0 [ESMS calcd. for $(M + Na)^+$]

[a] Reaction carried out using HATU. [b] Mass calculated for $(M + K)^+$. [c] Reaction carried out using EDC-HOBt system.

We then focused on preparing *N*-protected α-amino acid azides which are the common precursors for peptide as well as peptidomimetic synthesis. Our group has reported the synthesis of Fmoc-α-amino acid azides using acid chlorides and mixed anhydrides.[2c] These azides were isolated as shelf stable compounds and were used as peptide coupling agents. In the present study, for the conversion of α-amino acids into acid azides, HBTU was used, although better results were obtained with EDC in our above study. Usage of EDC alone causes an appreciable degree of racemization during activation, which has to be minimized by using additives like HOBt. This generates the same -OBt active ester as the acylating agent as that of HBTU. Hence HBTU was directly used for the preparation of amino acid azides rather than EDC-HOBt. HBTU is also familiar to peptide chemists, involves a simple operational procedure and is less expensive than HATU. In a typical reaction, Fmoc-Phe-OH in THF at 0 °C was treated with an equivalent each of HBTU and diisopropylethylamine (DIEA) followed by the addition of NaN_3 in DMSO. Formation of the acyl azide was completed in about 15 min. A simple work-up led to the isolation of Fmoc-Phe-N_3 **4e** in 82% yield (EDC-HOBt system also yielded **4e** in a similar yield; Table 3). The reaction was repeated to prepare several Fmoc amino acid azides **4a–d** and **4f, g** and also Z-Phe-N_3. Acid azide **4h** which is the product of



Pg = Fmoc: **3a-f**; Pg = Z: **3g** Pg = Fmoc: **4a-f**; Pg = Z: **4g**

Scheme 2 Synthesis of N-protected α-amino acid azides **4**.

conversion of the β-COOH of Z-Asp-OH was prepared similarly from Z-Asp-5-oxazolidinone (Table 3).

One pot synthesis of ureas and carbamates

We could successfully synthesize, isolate and characterize a series of acid azides using HBTU and EDC. But several classes of acid azides such as N-Boc and Z protected α-amino acid azides are not stable towards isolation. Syntheses involving such acid azides can be efficiently carried out through one-pot synthetic procedures which involve the chemical transformation of the acid azides generated *in situ* without isolation. These one pot protocols are also highly useful for rapid synthesis of biologically active analogues which are required in large numbers for screening. An example of such kind is the single-pot synthesis of ureas and carbamates starting from acids which involves the formation of acid azides and their *in situ* Curtius rearrangement followed by coupling of the isocyanates with amines and alcohols. Procedures for generating acid azides using NaN_3 and chloroformates or Boc_2O, and the rearrangement and trapping of the isocyanates in presence of *n*-Bu_4NBr and zinc triflate, have been reported.[29,30] A continuous flow reactor designed for the sequential execution of the generation and rearrangement of acid azides, and coupling of isocyanates has also been used to prepared ureas and carbamates.[31] DPPA and Deoxo-Fluor-TMS-N_3 have been employed in the preparation of peptidyl and sugar ureas.[17b,17d] However, application of the peptide coupling agents for this purpose has not been demonstrated. We extended the utility of EDC and HBTU to the one-pot synthesis of ureas and alkyl carbamates. Accordingly, Fmoc-Phe-OH was treated with HBTU in THF for 30 min and then refluxed till the complete formation of isocyanate (IR), followed by coupling with the ester H-Ala-OMe. This yielded the dipeptidyl urea **5b** which was purified by recrystallization with DMSO-water and characterized. Using this procedure, several dipeptidyl ureas **5a**, **5c–f** were synthesized from Fmoc, Boc and Z-amino acids (Scheme 3, Table 4). Urea-peptide hybrids, Fmoc-Val-Ala-ψ[NH-CO-NH]-Val-OMe (**5f**) and Fmoc-Pro-Val-ψ[NH-CO-NH]-Val-OMe (**5g**) were also obtained from the corresponding Fmoc-dipeptide acids. Further, when the *in situ* generated isocyanates were treated with 2.0 equivalents of methanol, methyl carbamates **6a–e** were obtained in 75–93% yield (Table 4). Similarly, when, *p*-nitrobenzoic acid and thiophene-2-carboxylic acid were reacted with NaN_3, EDC at 0 °C in CH_2Cl_2 for 20 min followed by refluxing in the presence of ethanol and toluene, the ethyl carbamates **6g** and **6f** were obtained. Addition of amines under similar condition resulted in ureas **5h–n** from diversely functionalized acids (Table 4).

One-pot synthesis of the ureas and carbamates was also carried out under ultrasonication. Ureas **5a**, **5c–e** and carbamates **6a** and **6e** were synthesized *via* the rearrangement of acid azides as well as the coupling of the resulting isocyanates at rt under the influence of ultrasonic waves (Scheme 3; method c). The yields of the compounds thus prepared were comparatively higher (Table 4) and also the reaction could be carried out at rt with the same reaction duration.

In conclusion, we have demonstrated the first application of the peptide coupling agents for the direct conversion of acids into acid azides. The use of carbodiimide EDC and the uronium reagent HBTU as carboxylic activator has resulted in a mild, facile and racemization free synthesis[32] of acid azides from a diverse range of acids including N-Fmoc/Z-protected α-amino acids. All the azides have been obtained in good yields. The coupling agents have also been successfully employed for the one-pot synthesis of ureas and carbamates from acids.

Experimental section

General procedure for the preparation of acyl azides 2

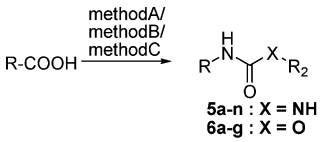
To a solution of an acid (1.0 mmol) in dry CH_2Cl_2 (10.0 mL) was added EDC (1.1 mmol, 210.2 mg) at 0 °C followed by NaN_3 (97.5 mg, 1.5 mmol) in DMSO (1 mL). The reaction mixture was stirred for 20 min. It was diluted with CH_2Cl_2 and the organic layer (15.0 mL) was washed with 5% sodium carbonate (2 × 10 mL), water (2 × 10 mL), and brine (10 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated *in vacuo* to obtain the products.

General procedure for the preparation of Fmoc/Z amino acid azides 4

To a solution of Fmoc/Z-amino acid (1.0 mmol) in dry THF (10.0 mL) were added DIEA (1.3 mmol) and HBTU (1.1 mmol, 148.5 mg) at 0 °C followed by NaN_3 (97.5 mg, 1.5 mmol) in DMSO (1 mL). The reaction mixture was stirred for 20 min, concentrated *in vacuo* and the residue was flash chromatographed (20% EtOAc in hexane) to obtain pure acid azides.

General procedure for the synthesis of ureas and carbamates 5h–n and 6f, g

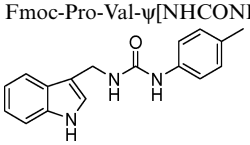
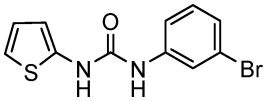
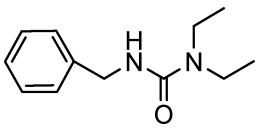
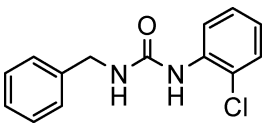
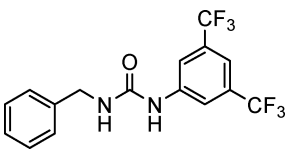
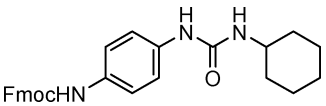
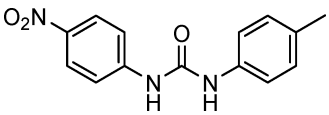
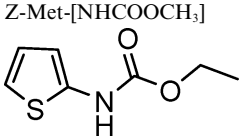
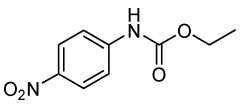
To a solution of acid (1.0 mmol) in dry CH_2Cl_2, EDC (1.1 mmol, 210.2 mg) was added at 0 °C followed by NaN_3 (1.5 mmol) in DMSO (1 mL) and stirred for 15 min. Toluene was added to the reaction mixture which was then refluxed for 30 min followed by the addition of 1.0 mmol of an amine or ethanol, and the refluxing was continued till the completion of the reaction. The



method A : i) HBTU, DIEA, NaN_3/DMSO, 0 °C, 25 min, THF; ii) amine or alcohol, reflux, 30 min
method B : i) EDC, NaN_3/DMSO, 0 °C, 15 min, CH_2Cl_2; ii) amine or alcohol, toluene reflux
method C: i) HBTU, DIEA, NaN_3/DMSO, 0 °C, 25 min,THF; ii) amine or alcohol, ultrasonication, 30 min

Scheme 3 Synthesis of ureas and carbamates.

Table 4 List of ureas and carbamates prepared *via* Scheme 3

Compd.	Ureas/carbamates	Yield (%)	M.p./°C	HRMS: Found/Calcd. $(M + Na)^+$
5a[a]	Fmoc-Ala-ψ[NHCONH]-Val-OMe	80 (88)	181	462.2008/462.2005
5b[a]	Fmoc-Phe-ψ[NHCONH]-Ala-OMe	81	186	510.2010/510.2005
5c[a]	Boc-Val-ψ[NHCONH]-Ala-OMe	76 (85)	168	340.1825/340.1848
5d[a]	Boc-Leu-ψ[NHCONH]-Val-OMe	79 (86)	175	382.2313/382.2318
5e[a]	Cbz-Ala-ψ[NHCONH]-Gly-OMe	75 (90)	142	332.1/332.1 (ESMS calcd. for M + Na)
5f[a]	Fmoc-Val-Ala-ψ[NHCONH]-Leu-OMe	73	170	575.2853/575.2846
5g[a]	Fmoc-Pro-Val-ψ[NHCONH]-Val-OMe	81	*gum*	559.2539/559.2533
5h[b]		75	125	280.1445/280.1450[c]
5i[b]		79	245	320.9506/320.9435
5j[b]		77	*gum*	229.1321/229.1317
5k[b]		83	*gum*	261.0797/261.0794[c]
5l[b]		82	184	363.0943/363.0932[c]
5m[b]		72	174	478.2114/478.2107
5n[b]		74	188	294.0852/294.0855
6a[a]	Fmoc-Gly-[$NHCOCH_3$]	75 (88)	145	349.1168/349.1164
6b[a]	Fmoc-Leu-[$NHCOOCH_3$]	80	172	405.1793/405.1790
6c[a]	Fmoc-Phe-[$NHCOOCH_3$]	78	190	439.1620/439.1634
6d[a]	Z-Val-[$NHCOOCH_3$]	75	138	303.1341/303.1433
6e[a]	Z-Met-[$NHCOOCH_3$]	79 (84)	130	335.1039/335.1041
6f[a]		78	*gum*	172.0428/172.0432[c]
6g[a]		86	93	233.0542/233.0538

[a] Prepared by method A in Scheme 3. [b] Prepared by method B in Scheme 3; values in parenthesis are the yields for method C in Scheme 3. [c] Mass calcd. for $(M + H)^+$.

solvent was evaporated and the residue was dissolved in EtOAc. The organic layer was washed with 20% Na_2CO_3 followed by HCl, water and brine, dried with anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain the crude product which was purified through column chromatography (30% EtOAc in hexane)

General procedure for the synthesis of ureas and carbamates 5a–g and 6a–e

To a solution of acid (1.0 mmol) in dry THF, DIEA (1.0 mmol) and HBTU (1.1 mmol, 148.5 mg) were added at 0 °C followed by NaN_3 (1.5 mmol) in DMSO (1 mL) and stirred for 25 min. It was then refluxed or ultrasonicated for 30 min followed by the addition of 1.0 mmol of an amino acid ester or an alcohol and the refluxing or ultrasonication was continued till the completion of the reaction. The solvent was then evaporated and resultant residue was washed with water. The crude product was purified through recrystallization from DMSO-water.

Characterization data for representative compounds

2-(1*H*-Indol-3-yl)acetyl azide, 2e. R_f 0.4 (n-hexane–AcOEt 8 : 2); IR (KBr) $\nu_{max} = 2138\ cm^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.86 (2H, s), 7.02 (1H, d, $J = 2.0$ Hz), 7.05–7.59 (4H, m), 8.84 (1H, s); ^{13}C NMR ($CDCl_3$,100 MHz) δ 31.84, 111.81, 111.93, 120.03, 122.50, 123.74, 123.89, 127.69, 136.69, 172.83; HRMS Calc'd for $C_{10}H_8N_4O$ *m/z*: 201.0776 (M^+ + H), found 201.0781

(*S*)-Methyl 2-(3-((*R*)-1-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy)-carbon-yl)-3-methylbutanamido)ethyl)ureido)-4-methylpentanoate {Fmoc-Val-Ala-ψ[NHCONH]-Leu-OMe}, 5f. R_f 0.4 ($CHCl_3$–MeOH 9 : 1); IR (KBr) $\nu_{max} = 1652\ cm^{-1}$; ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.81 (6H, br), 1.08 (6H, br), 1.18 (2H, m), 2.52–2.63 (2H, br), 3.53 (3H, s), 4.23 (1H, m) 4.41–4.52 (2H, m), 4.62 (2H, d, $J = 7.0$ Hz), 5.09 (1H, m), 6.32 (1H, br), 7.89–7.21 (8H, m); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.99, 20.20, 24.18, 25.30, 31.00, 35.00, 47.55, 55.34, 56.17, 61.03, 66.60, 126.27, 128.02, 128.60, 129.88, 141.58, 144.76, 156.30, 157.10, 171.35, 174.39; HRMS Calc'd for $C_{30}H_{40}N_4O_6$ *m/z*: 575.2846 (M^+ + Na), found 575.2853

Ethyl thiophen-2-ylcarbamate, 6f. R_f 0.4 (n-hexane–AcOEt 7 : 3); IR (KBr) $\nu_{max} = 1728\ cm^{-1}$; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.25 (3H, t, $J = 7.24$ Hz), 4.21 (2H, q, $J = 6.8$ Hz), 6.60–6.78 (3H, m), 8.10 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.98, 62.37, 112.80, 117.68, 125.15, 140.69, 154.59, HRMS Calc'd for $C_7H_9NO_2S$ *m/z*: 172.0432 (M^+ + H), found 172.0428

Acknowledgements

We thank Department of Science and Technology (Grant no. SR/S1/OC/26/2008) and Council of Scientific and Industrial Research, Govt. of India for financial support. H. S. L. thanks Siddaganga Institute of Technology, Tumkur, India for research leave.

References

1 (*a*) S. Brase, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188–5240 and references cited therein; (*b*) E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 297–368 and references therein.

2 For peptide synthesis using acid azides see: (*a*) J. Lutz, H.-J. Musiol, and L. Moroder, Vol. E22a, pp 427 in *Houben-Weyl: Synthesis of Peptides & Peptidomimetics*, M. Goodman, A. Felix, L. Moroder and C. Toniolo, ed.; Georg Thieme Verlag: Stuttgart, New York; For the utility of Boc/Z-amino acid azides in total synthesis of ribonuclease in solution, see: (*b*) N. Fujii and H. J. Yajima, *J. Chem. Soc., Perkin Trans. 1*, 1981, 831–841 and references cited therein; For Fmoc-acid azides as peptide coupling agents see: (*c*) V. V. Suresh Babu, K. Ananda and G. R. Vasanthakumar, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4328–4331; For applications of acids azides in peptidomimetics synthesis see: (*d*) M. Chorev, *Biopolymers Peptide Sci*, 2005, **80**, 67–84; (*e*) M. D. Fletcher and M. M. Campbell, *Chem. Rev.*, 1998, **98**, 763–795.

3 C. O. Kangani, B. W. Day and D. E. Kelley, *Tetrahedron Lett.*, 2008, **49**, 914–918.

4 (*a*) A. Palani, S. Shapiro, M. D. McBriar, J. W. Clader, W. J. Greenlee, B. Spar, T. J. Kowalski, C. Farley, J. Cook, M. Van Heek, B. Weig, K. O'Neill, M. Graziano and B. Hawes, *J. Med. Chem.*, 2005, **48**, 4746–4749; (*b*) J. R. Merritt, J. Liu, E. Quadros, M. L. Morris, R. Liu, R. Zhang, B. Jacob, J. Postelnek, C. M. Hicks, W. Chen, E. F. Kimble, W. L. Rogers, L. O'Brien, N. White, H. Desai, S. Bansal, G. King, M. J. Ohlmeyer, K. C. Appell and M. L. Webb, *J. Med. Chem.*, 2009, **52**, 1295–1301.

5 (*a*) B. S. Patil, G. R. Vasanthakumar and V. V. Suresh Babu, *J. Org. Chem.*, 2003, **68**, 7274–7280; (*b*) V. V. Sureshbabu, B. S. Patil and R. Venkataramanarao, *J. Org. Chem.*, 2006, **71**, 7697–7705; (*c*) L. Fischer, V. Semetey, J.-M. Lozano, A.-P. Schaffner, J.-P. Briand, C. Didierjean and G. Guichard, *Eur. J. Org. Chem.*, 2007, 2511–2525; (*d*) G. Guichard, V. Semetey, C. Didierjean, A. Aubry, J.-P. Briand and M. Rodriguez, *J. Org. Chem.*, 1999, **64**, 8702–8705; (*e*) G. Guichard, V. Semetey, M. Rodriguez and J.-P. Briand, *Tetrahedron Lett.*, 2000, **41**, 1553–1557.

6 (*a*) J. M. Bermann and M. Goodman, *Int. J. Pept. Prot. Res.*, 1984, **23**, 610–620; (*b*) M. Chorev and M. Goodman, *Int. J. Pept. Prot. Res.*, 1983, **21**, 268–265; For the synthesis of amino alkyl formamides see: (*c*) N. S. Sudarshan, N. Narendra, H. P. Hemantha and V. V. Sureshbabu, *J. Org. Chem.*, 2007, **72**, 9804–9807; (*d*) V. V. Sureshbabu, N. Narendra and G. Nagendra, *J. Org. Chem.*, 2009, **74**, 153–157; For unnatural amino acids see: (*e*) E. A. Englund, H. N. Gopi and D. H. Appella, *Org. Lett.*, 2004, **6**, 213–215.

7 For selected reports see: (*a*) P. W. Erhardt, *J. Org. Chem.*, 1979, **44**, 883–884; (*b*) G. W. Rewcastle and W. A. Denny, *Synthesis*, 1985, 220–222; (*c*) A. E. Luedtke and J. W. Timberlake, *J. Org. Chem.*, 1985, **50**, 268–270; (*d*) A. Padwa, M. A. Brodney, B. Liu, K. Satake and T. Wu, *J. Org. Chem.*, 1999, **64**, 3595–3607; (*e*) C. K. Govindan, *Org. Process Res. Dev.*, 2002, **6**, 74–77; For the use of HN_3/pyridine: (*f*) J. M. Lemmens, W. W. J. M. Blommerde, L. Thijs and B. Zwanenburg, *J. Org. Chem.*, 1984, **49**, 2231–2235.

8 For selected reports see: (*a*) M. Chorev, S. A. MacDonald and M. Goodman, *J. Org. Chem.*, 1984, **49**, 821–827; (*b*) C. Bolm, C. L. Dinter, I. Schiffers and L. Defrere, *Synlett*, 2001, 1875–1877; (*c*) E. A. Englund, H. N. Gopi and D. H. Appella, *Org. Lett.*, 2004, **6**, 213–215; (*d*) R. K. Boekman and L. M. Reeder, *Synlett*, 2004, 1399–1405; (*e*) P. H. Dussault and Chunping Xu, *Tetrahedron Lett.*, 2004, **45**, 7455–7457.

9 J. R. Pfister and W. E. Wymann, *Synthesis*, 1983, 38–39.

10 G. K. Surya Prakash, P. S. Iyer, M. Arvanaghi and G. A. Olah, *J. Org. Chem.*, 1983, **48**, 3358–3359.

11 A. Padwa, K. R. Crawford, P. Rashatasakhon and M. Rose, *J. Org. Chem.*, 2003, **68**, 2609–2617.

12 B. P. Bandgar and S. S. Pandit, *Tetrahedron Lett.*, 2002, **43**, 3413–3414.

13 V. K. Gumaste, B. M. Bhawal and A. R. A. S. Deshmukh, *Tetrahedron Lett.*, 2002, **43**, 1345–1346.

14 H. Eilingsfeld, M. Seefelder and H. Weidinger, *Angew. Chem.*, 1960, **72**, 836–845.

15 A. R. Katritzky, K. Widyan and K. Kirichnko, *J. Org. Chem.*, 2007, **72**, 5802–5804.

16 (*a*) M. Bodanszky, and A. Bodanszky, *The practice of peptide synthesis*. Springer Verlag, Berlin, 1984, p. 91; (*b*) J. E. Macor, G. Mullen, P. Verhoest, A. Sampognaro, B. Shepardson and R. A. Mack, *J. Org. Chem.*, 2004, **69**, 6493–6495; (*c*) M. Nettekoven and C. Jenny, *Org. Process Res. Dev.*, 2003, **7**, 38–43.

17 For reports on DPPA see: (*a*) M. R. Pawia, S. J. Lobbestael, C. P. Taylor, F. M. Hershenson and D. L. Miskell, *J. Med. Chem.*, 1990, **33**, 854–861; (*b*) V. V. Sureshbabu, G. Chennakrishnareddy and N. Narendra, *Tetrahedron Lett.*, 2008, **49**, 1408–1412; For reports on Deoxo-Flour/NaN_3 see: (*c*) C. O. Kangani, B. W. Day and D. E.

Kelley, *Tetrahedron Lett.*, 2007, **48**, 5933–5937; (*d*) H. P. Hemantha, G. Chennakrishnareddy, T. M. Vishwanatha and V. V. Sureshbabu, *Synlett*, 2009, 407–410.
18 D. Subhas Bose and A. V. Narasimha Reddy, *Tetrahedron Lett.*, 2003, **44**, 3543–3545.
19 (*a*) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606–631 and references cited therein; (*b*) J. Podlech, Vol E22a, pp 517–533 in *Houben-Weyl: Synthesis of Peptides & Peptidomimetics* M. Goodman, A. Felix, L. Moroder and C. Toniolo, ed., Georg Thieme Verlag: Stuttgart, New York, 2003; (*c*) H. G. Khorana, *Chem. Rev.*, 1953, **53**, 145–166; (*d*) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 1955, **77**, 1067–1068.
20 *Houben-Weyl: Synthesis of Peptides & Peptidomimetics*, M. Goodman, A. Felix, L. Moroder and C. Toniolo, ed., Georg Thieme Verlag: Stuttgart, New York, 2003; Vol. E22a and references cited therein; L. A. Carpino, *J. Am. Chem. Soc.*, 1993, **115**, 4397–4398.
21 (*a*) C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827–10852; For applications of peptide couplings PyBrOP/polymer supported reagent/HOBt used in the flow synthesis of tripeptides see: (*b*) I. R. Baxendale, S. V. Ley, C. D. Smith and G. K. Tranmer, *Chem. Commun.*, 2006, 4835–4837.
22 For a review on peptide coupling reagents in organic synthesis, see: (*a*) S.-Y. Han and Y.-A. Kim, *Tetrahedron*, 2004, **60**, 2447–2467 and references cited therein; (*b*) D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, S. L. Castle and O. Loiseleur, *J. Am. Chem. Soc.*, 1999, **121**, 10004–10011; (*c*) B. Cao, H. Park and M. M. Joullie, *J. Am. Chem. Soc.*, 2002, **124**, 520–521.
23 W. Konig and R. Geiger, *Chem. Ber.*, 1970, **103**, 2034–2040.
24 E. Wunsch and F. Drees, *Chem. Ber.*, 1966, **99**, 110.
25 W. Konig and R. Geiger, *Chem. Ber.*, 1970, **103**, 788–798.
26 (*a*) D. S. Tarbell, Y. Yamamoto and B. M. Pope, *Proc. Natl. Acad. Sci. U. S. A.*, 1972, **69**, 730–732; (*b*) V. F. Pozdnev, *Khim. Prir. Soedin.*, 1971, 384; (*c*) O. Keller, W. E. Keller, G. Van Looka and G. Werson, *Org. Synth.*, 1985, **63**, 160.
27 M. Nagarajan, V. S. Kumar and B. V. Rao, *Tetrahedron Lett.*, 1997, **38**, 5835–5838.
28 D. K. Mohapatra and A. Datta, *J. Org. Chem.*, 1999, **64**, 6879–6880.
29 H. Lebel and O. Leogane, *Org. Lett.*, 2005, **7**, 4107–4110.
30 H. Lebel and O. Leogane, *Org. Lett.*, 2006, **8**, 5717–5720.
31 (*a*) M. Baumann, I. R. Baxendale, S. V. Ley and N. C. D. Nikbin Smith, *Org. Biomol. Chem.*, 2008, **6**, 1587–1593; (*b*) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith and J. P. Tierney, *Org. Biomol. Chem.*, 2008, **6**, 1577–1586.
32 Optical purities of the ureas were determined by the NMR analysis of compounds, Boc-Phe-ψ[NHCONH]-(*R*)-1-phenylethylamine **7a** and Boc-Phe-ψ[NHCONH]-(*S*)-1-phenylethylamine **7b** prepared by reacting Boc-Phe-OH with (*R*) and (*S*) 1-phenylethylamine separately *via* method A in Scheme 3, contained the methyl group doublets at $\delta = 1.27, 1.29$; and 1.24, 1.26 respectively. The equimolar mixture of these compounds obtained by reacting racemic 1-phenylethylamine with Boc-Phe-OH had -CH_3 peaks at 1.24, 1.26, 1.27, 1.29 ppm, corresponding to the presence of two epimers. These studies confirmed that the sample **7a** and **7b** contained a single and optically pure compound. Thus using the present method, acid azides as well as ureas/carbamates can be prepared with no significant racemization.

