3,3-Dichloro-1,2-diphenylcyclopropene (CPICl)-Mediated Synthesis of N^{α}-Protected Amino Acid Azides and α-Ureidopeptides

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Abstract: Rapid synthesis of acid azides via in situ generation of acid chlorides using CPICl as chlorinating agent from the corresponding N^{α}-protected amino acids is described. Also the conversion of acid azides into ureidopeptides through the Curtius rearrangement under ultrasonication is delineated. The mildness of the protocol renders the acid-sensitive substrates to afford the corresponding amino acid azides and ureidopeptides in good yields. Diphenylcyclopropenone has also been recovered from the reaction mixture and reused.

Keywords: N^{α}-protected amino acids, CPICl, acid chlorides, acid azides, Curtius rearrangement, ureidopeptides

In recent years acid azides have gained more importance in peptide chemistry, combinatorial chemistry, and heterocyclic synthesis. The Curtius rearrangement of acid azides lead to isocyanates, from which amines, urethanes, thiourethanes, ketenimines, carbodiimides, carbamates, and ureas can be easily obtained.[1] Accordingly, there has been a significant amount of effort directed at developing efficient methods for the synthesis of acid azides either direct or indirectly from carboxylic acids.

Direct conversion of carboxylic acids into acid azides is achieved using acid activators such as phenyl dichlorophosphate,[2a] $SOCl_2$-DMF,[2b] ethyl chloroformate,[2c] NCS-Ph_3P,[2d] diphenylphosphoryl azide (DPPA),[2e] cyanuric chloride,[2f] triphosgene,[2g] $POCl_3$-DMF,[2h] bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor),[2i] Cl_3CCN/Ph_3P,[2j] benzotriazole-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP),[2k] 2-azido-1,3-dimethyl-imidazolinium chloride (ADMC),[2l] Ph_2PCl/I_2,[2m] 3,4,5-trifluorobenzeneboronic acid,[3] di-*tert*-butyl dicarbonate,[4] trichloroisocyanuric acid/Ph_3P[5] in the presence of NaN_3/$TMSN_3$. These protocols often suffer from several limitations, which include harsh reaction conditions, substrate limitations, elevated temperatures, prolonged reaction duration, offensive byproduct formation, etc.

Acid azides can also be prepared from acid derivatives such as acid chlorides,[6] mixed anhydrides,[7] acyl hydrazides,[8] and acyl benzotriazoles.[9] Synthesis of Fmoc-α-amino acid azides using acid chlorides and mixed anhydrides had been reported by our group.[10] The acid chloride method has disadvantages such as preparation and storage of acid chloride itself. The HCl generated with the usage of chlorinating reagents render them incompatible with acid-sensitive substrates (Boc/Z). Moreover, acid chlorides are sensitive to moisture, which require care in handling with sodium azide in aqueous conditions. Also the poor solubility of NaN_3 in organic reaction medium requires the usage of phase-transfer catalyst to improve the yield of acid azides.[11] Mixed anhydride method involves the use of alkyl chloroformates which are inconvenient to handle. For the synthesis of acid azides, acyl hydrazides need to react with nitrosyl ions or their precursors. Acyl benzotriazoles preparation proceeded with longer reaction duration. Aldehydes have also been directly converted into acid azides using chromic anhydride and trimethylsilylazide,[12a] (diacetoxyiodo)benzene (DIB),[12b] triazidochlorosilane-activated MnO_2,[12c] IN_3,[12d] *tert*-butyl hypochlorite,[12e] Dess–Martin periodinane,[12f] 1,3-dimethyltriazolium iodide–diazabicycloundecane (DBU).[12g]

Since acid chlorides are attractive to accomplish activation of a carboxylic group towards acylation, it is desirable to develop a newer protocol devoid of sulfur- or phosphorus-based catalysts, aqueous and harsh conditions including elevated temperature. In continuation of our works, herein we report a mild and highly efficient procedure using CPICl/$TMSN_3$ for the synthesis of N^{α}-protected amino acid azides from the corresponding carboxylic acids and their conversion into ureidopeptides. Significantly, the protocol is compatible with acid-labile protecting groups.

The cyclopropenium cation is the smallest member of the Hückel aromatic systems, and numerous investigations have been carried out on this class of cation since the first synthesis of triphenylcyclopropenylium perchlorate by Breslow.[13] Particularly in organometallic chemistry these cations have been developed in various applications.[14] Recently, Lambert et al. developed the reactions involving cyclopropenium intermediates, for the rapid conversion of alcohols and carboxylic acids into the corresponding alkyl chlorides[15a] and acid chlorides.[15b] The similar strategy was applied for the dehydrative cyclization of diols to cyclic ethers and nucleophilic substitution of alcohols by methane sulfonate ion with inversion of configuration by the same group.[16] The concept of cyclopropenium activation has been extended to Beckman rearrangement of ketoximes to amides/lactams.[17] Bennett et al. described dehydrative glycosylation reactions using deoxy- and di-

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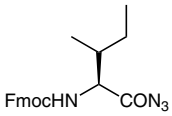
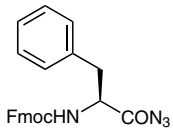
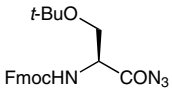
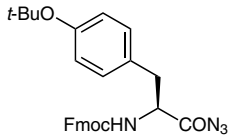
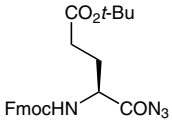
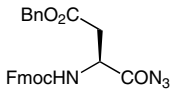
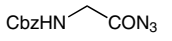
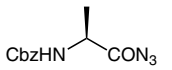
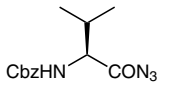
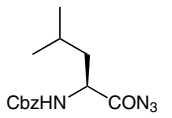
deoxy-sugar donors mediated by dichlorodiphenylcyclopropene which is tolerant of acid- and base-sensitive substrates.[18]

Attracted by the unique reactivity profile of the cyclopropenium ion, we envisioned that cyclopropenium activation might be the rapid and mild process for the conversion of carboxylic acids into acid azides via the intermediacy of acid chlorides. In a typical reaction, to the in situ generated 3,3-dichloro-1,2-diphenylcyclopropene (generated by the treatment of 2,3-diphenylcyclopropenone with oxalyl chloride in CH_2Cl_2),[19] a solution of Fmoc-Ile-OH (**1a**) and diisopropylethylamine (DIPEA) in dry CH_2Cl_2 was added at –15 °C. After five minutes, $TMSN_3$ was added to the reaction mixture. As monitored by TLC, the desired acid azide was obtained within 5–10 minutes and was confirmed by IR analysis showing strong absorbance at 2141 cm^{-1}. A simple workup led to Fmoc-Ile-CON_3 (**2a**) and diphenylcyclopropenone. Other solvents such as MeCN, THF, 1,4-dioxane, and EtOAc were tried and found to be inefficient in affording the desired product in good yields. Dichloromethane in the presence of DIPEA was found to be the best reaction medium for the easier isolation of acid azides at lower temperatures. The crude residue was purified by flash chromatography (20% EtOAc in hexane) to obtain pure Fmoc-Ile-CON_3 (**2a**).[20,27] Diphenylcyclopropenone was recovered quantitatively (Scheme 1).

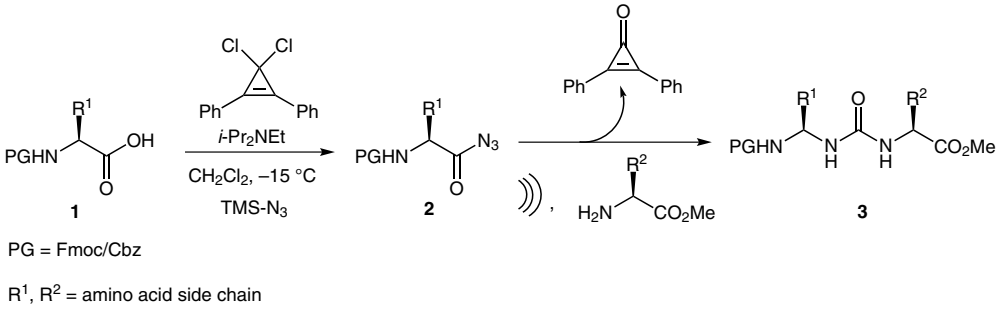
Since acid azides are valuable synthetic intermediates in peptide chemistry, we further explored them for the synthesis of ureidopeptides through the Curtius rearrangement. Fmoc-Ile-CON_3 (**2a**) was subjected to ultrasonication using our reported procedure.[21] Subsequently, the formed isocyanate was treated with methyl glycinate, and the ultrasonication was continued till completion of the reaction. After a simple workup, the solvent was removed in vacuo. The crude product was recrystallized (DMSO–H_2O, 8:2) to obtain the ureidopeptide **3a** (Scheme 1). To explore the scope and generality of the method, various N^{α}-Fmoc/Cbz-amino acids were tested for the nucleophilic substitution with $TMSN_3$ via in situ generation of acid chlorides, and their application for the synthesis of ureidopeptides through the Curtius rearrangement. The results are summarized in Table 1 and Table 2.

One-pot processes that allow the direct conversion of carboxylic acids into ureas have become attractive. Guichard et al. reported the one-pot conversion of *N*-Boc-protected β-amino acids to acyl azides and then to carbamates.[22] Sureshbabu and his coworkers prepared ureas and carbamates from the corresponding carboxylic acids using EDC

Table 1 List of N^{α}-Fmoc/Cbz-Amino Acid Azides **2**

Compound	Acid azide **2**	Yield (%)[a]	mp (°C)
2a		94	152
2b		96	175
2c		93	178
2d		92	173
2e		90	168
2f		93	135
2g		91	67
2h		93	123
2i		92	130
2j		94	134

[a] Yields correspond to the isolated pure acid azides.



Scheme 1 Synthesis of N^{α}-Fmoc/Cbz-amino acid azides **2** and their conversion into the corresponding ureidopeptides **3**

Table 2 List of *N*$^{\alpha}$-Fmoc/Cbz-Ureidopeptides **3**

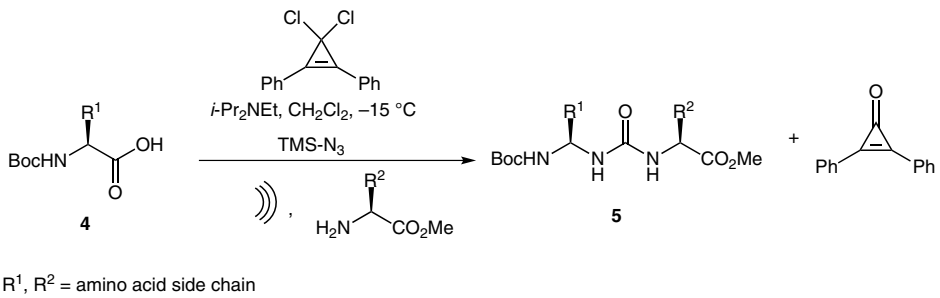
Compound	PG	R^1	R^2	Yield (%)
3a	Fmoc	CH(Me)Et	H	92
3b	Fmoc	Bn	Me	89
3c	Fmoc	CH_2O*t*-Bu	H	90
3d	Fmoc	$CH_2C_6H_4O$*t*-Bu	*i*-Pr	92
3e	Fmoc	$CH_2CH_2CO_2$*t*-Bu	H	91
3f	Fmoc	CH_2CO_2Bn	*i*-Pr	93
3g	Cbz	H	*i*-Pr	89
3h	Cbz	Me	H	91
3i	Cbz	*i*-Pr	Me	92
3j	Cbz	CH_2CHMe_2	Me	93

and HBTU.[23] Due to the instability of *N*$^{\alpha}$-Boc-amino acid azides, we further investigated the optimized reaction conditions for the one-pot synthesis of α-ureidopeptides starting from Boc-amino acids. The process involves the formation of acid azides via the intermediacy of acid chloride and their in situ Curtius rearrangement to an isocyanate followed by coupling with amino acid methyl ester under ultrasonication. The Boc-Phe-OH (**4d**) was treated with CPICl/$TMSN_3$ and DIPEA at –15 °C in CH_2Cl_2. After completion of reaction as monitored by IR (ν_{max} = 2140 cm^{-1}), the reaction mixture was subjected to ultrasonication for about 20 minutes. Subsequently, L-methyl alaninate was added, and the ultrasonication was continued till completion of the reaction. The solvent was evaporated, and the residue was washed with citric acid and $NaHCO_3$ solutions and triturated with diethyl ether and then filtered. The solid thus obtained was recrystallized (DMSO–H_2O) to obtain pure ureidopeptide[24] **5d** in good yield (Scheme 2). The diphenylcyclopropenone was also recovered from the ether layer. As summarized in Table 3, the reaction proceeded well with various *N*$^{\alpha}$-Boc-amino acids to afford the corresponding α-ureidopeptides in good yields. The Curtius rearrangement was monitored through IR by observing the disappearance of the azide peak at 2140 cm^{-1} and the appearance of the characteristic isocyanate peak at 2250 cm^{-1}. The same protocol holds good even for the one-pot synthesis of Fmoc/Cbz-protected α-ureidopeptides from the corresponding α-amino acids in reasonably good yields. The present protocol is an advantageous and alternative to the reported one-pot synthesis of ureidopeptides since phosphorous residues resulted from DPPA[25a] renders the product isolation a tedious process, T3P[25b] is moisture-sensitive and requires careful handling to obtain ureidopeptides. Unlike in situ generated acid chloride protocols for the synthesis of acid azides and then to ureidopeptides, the present protocol is compatible with Fmoc/Boc/Cbz chemistry. The ^{1}H NMR spectroscopy of the diastereomeric α-ureidopeptides, Boc-(L)-Phe-Ψ(NH-CO-NH)-(*R*)-(+)-1-phenylethylamine (**5k**), Boc-(L)-Phe-Ψ(NH-CO-NH)-(*S*)-(–)-1-phenylethylamine (**5l**), and Boc-(L)-Phe-Ψ(NH-CO-NH)-(*R*,*S*)-(±)-1-phenylethylamine (**5k** + **5l**) prepared by the present methodology, was found to be free from racemization.[26]

Table 3 List of *N*$^{\alpha}$-Boc-Ureidopeptides **5**

Compound	R^1	R^2	Yield (%)
5a	*i*-Pr	Me	89
5b	Me	Bn	88
5c	*i*-Pr	H	87
5d	Bn	Me	89
5e	*i*-Pr	Bn	90
5f	CH_2CH_2SMe	Bn	88
5g	CH(Me)OBn	Me	86
5h	$CH_2CH_2CO_2Bn$	*i*-Pr	87
5i	Ph	Me	90
5j	CH_2OBn	H	87

In conclusion, we have developed a mild and convenient protocol for the synthesis of N$^{\alpha}$-protected amino acid azides from the corresponding carboxylic acids using CPICl/$TMSN_3$ and their application for the synthesis of ureidopeptides through the Curtius rearrangement was found to be racemization-free. Using this protocol, several ureidopeptides were synthesized from Boc-, Cbz-, and Fmoc-amino acids including Asp, Glu, Ser, and Tyr possessing *tert*-butyl, benzyl, and Boc groups in the side chain.



R^1, R^2 = amino acid side chain

Scheme 2 Synthesis of *N*$^{\alpha}$-Boc-ureidopeptides **5**

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(20) **General Procedure for the Synthesis of *N*$^{\alpha}$-Fmoc/Cbz-Amino Acid Azides 2**
Oxalyl chloride (1.0 equiv) was added to a solution of diphenylcyclopropenone (1.1 equiv) in CH_2Cl_2 at r.t. After gas evolution had ceased, a solution of N$^{\alpha}$-protected amino acid (1.0 equiv) and DIPEA (2.2 equiv) in CH_2Cl_2 was added at –15 °C followed by stirring for 5 min and then $TMSN_3$ (1.5 equiv) was added. After stirring for an additional 5–10 min, the reaction mixture was diluted with CH_2Cl_2, washed with citric acid (10%), sat. $NaHCO_3$ (10%), and sat. NaCl solutions. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (20% EtOAc in hexane) to obtain pure acid azide. Diphenylcyclopropenone was recovered in approximately the same yield.

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(24) **General Procedure for the Synthesis of *N*$^{\alpha}$-Boc/Cbz/Fmoc-Ureidopeptides 5**
Oxalyl chloride (1.0 equiv) was added to a solution of diphenylcyclopropenone (1.1 equiv) in CH_2Cl_2 at r.t. After gas evolution had ceased, a solution of N$^{\alpha}$-protected amino acid (1.0 equiv) and DIPEA (2.2 equiv) in CH_2Cl_2 was added at –15 °C followed by stirring for 5 min, $TMSN_3$ (1.5 equiv) was added to the reaction mixture. After stirring for an additional 5–10 min, toluene was added to the reaction mixture which was subjected to ultrasonication at 45 °C for about 20 min followed by addition of amino acid methyl ester, and the ultrasonication was continued until completion of the reaction. The solvent was removed in vacuo. The residue was washed with citric acid (10%) and $NaHCO_3$ (10%) solutions and triturated 2–3 times with Et_2O (5 mL) and filtered. The solid obtained was then recrystallized using DMSO–H_2O (8:2). The diphenylcyclopropenone was also recovered from ether layer and reused.

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(26) The possibility of the epimerization for the two epimeric ureidopeptides was analyzed through ^{1}H NMR spectroscopy, which were prepared from Boc-(L)-Phe-OH and optically pure (*R*)-(+)- and (*S*)-(–)-1-phenylethylamine using the present method. The ^{1}H NMR spectra of Boc-

(L)-Phe-Ψ(NHCONH)-(*R*)-(+)-1-phenylethylamine (**5k**) and Boc-(L)-Phe-Ψ(NHCONH)-(*S*)-(–)-1-phenylethylamine (**5l**) contained the (*R*)- and (*S*)-1-phenylethylamine methyl group doublet at δ = 1.28, 1.30 and 1.25, 1.27 ppm, respectively. Whereas Boc-(L)-Phe-Ψ(NHCONH)-(*R*,*S*)-(±)-1-phenylethylamine (**5k** + **5l**) contained two separate doublets at δ = 1.25, 1.27, 1.28, 1.30 ppm for (*R*,*S*)-(±)-1-phenylethylamine methyl groups (Figure 1). This clearly indicates that the present protocol is free of epimerization.

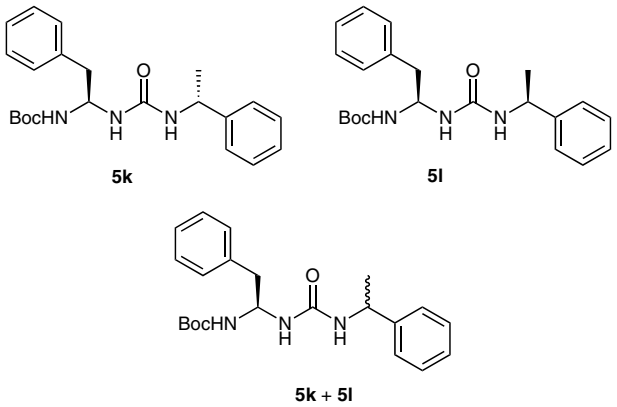

Figure 1

(27) **Selected Spectroscopic Data**

Fmoc-Ile-N$_3$ (2a)[23]

Yield 94%; mp 152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.88–0.92 (m, 3 H), 1.02–1.37 (m, 5 H), 1.87–1.99 (m, 1 H), 4.45–4.49 (m, 2 H), 4.54 (d, *J* = 6.3 Hz, 2 H), 5.14 (s, 1 H), 7.29–7.80 (m, 8 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.62, 15.10, 25.71, 30.03, 47.57, 55.82, 67.09, 120.49, 125.76, 127.67, 128.29, 141.58, 144.27, 156.63, 180.03. HRMS: *m/z* calcd for $C_{21}H_{22}N_4NaO_3$: 401.1590; found: 401.1596 [M + Na]$^+$.

(*Z*)-Ala-Ψ[NH-CO-NH]-Gly-OMe (3h)[23]

Yield 91%; mp 141–143 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.40 (d, *J* = 7.7 Hz, 3 H), 3.57 (s, 3 H), 4.45 (d, *J* = 6.5 Hz, 2 H), 5.13 (s, 2 H), 5.01–5.06 (m, 1 H), 5.66 (br, 1 H), 6.50 (br, 2 H), 7.22–7.38 (m, 5 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.56, 41.23, 51.49, 59.78, 64.94, 127.43, 127.61, 128.57, 137.22, 155.07, 156.28, 171.75. HRMS: *m/z* calcd for $C_{14}H_{19}N_3NaO_5$: 332.1222; found: 332.1225 [M + Na]$^+$.

Boc-Ser(Bn)-Ψ[NH-CO-NH]-Gly-OMe (5j)[24]

Yield 87%; mp 133 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.34 (s, 9 H), 3.44–3.48 (m, 2 H), 3.62 (s, 3 H), 3.84 (d, *J* = 6.9 Hz, 2 H), 4.49 (s, 2 H), 4.94–4.97 (m, 1 H), 5.78 (br, 1 H), 6.48 (br, 1 H), 6.54 (br, 1 H), 7.26–7.38 (m, 5 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.63, 45.51, 53.56, 71.57, 76.61, 77.45, 78.77, 126.61, 127.36, 128.53, 138.14, 156.38, 157.25, 171.35. HRMS: *m/z* calcd for $C_{18}H_{27}N_3NaO_6$: 404.1798; found: 404.1797 [M + Na]$^+$.