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An Efficient Conversion of the Carboxylic Group of *N*-Fmoc α-Amino Acids/Peptide Acids into *N*-Formamides Employing Isocyanates as Key Intermediates

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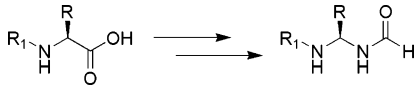

R_1 = Fmoc, Fmoc-Xaa.

Reaction of 96% formic acid with isocyanates derived from *N*-Fmoc α-amino acids/peptide acids catalyzed by DMAP has yielded a new class of stable formamides as crystalline solids which have been characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. Conversion of the side chain carboxylic acid of *N*-Fmoc-5-oxazolidinones of Asp/Glu into the *N*-formyl group also has been accomplished. The reaction is simple, mild, and high yielding.

N-Formamides represent a valuable class of compounds by virtue of their widespread applications in medicinal and organic chemistry. They are extensively used in the pharmaceuticals to make medically useful compounds like fluoroquinones,[1] imidazoles,[2] nitrogen bridged heterocycles,[3] etc. Formamides are the important entities in organic synthesis as they are starting materials for a variety of products such as formamidines,[4] monomethylated amines,[5] and isocyanides.[6] They also serve as useful reagents in the Vilsmeier formylation reactions,[7] asymmetric allylation,[8] and hydrosilylation of carbonyl compounds.[9] Further, the formyl group finds utility as both amino and hydroxyl protection in peptide synthesis.[10−12] *N*-Formyl amino acid esters can be dehydrated to the corresponding isonitriles[13] which are versatile starting materials for the synthesis of various bioactive compounds[14] and important components in Passerini's[15] as well as Ugi's multicomponent reactions.[16]

There are a large number of reports on formylation of the amino group including that of α-amino acid esters. These include the direct reaction with formic acid[17] or along with a catalyst like ZnO,[18] KF-Al_2O_3,[19] formylation with acetic formic anhydride,[20] chloral,[21] carbodiimide activated formic acid,[22] and ammonium formate.[23] In peptide chemistry, the reported formylation procedures[24] have targeted the conversion of the amino group of amino acid esters into *N*-formamides (Figure 1).

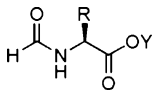

FIGURE 1. *N*-Formyl α-amino acid ester.

However, there has not been any report on the transformation of the carboxylic acid function of the N-protected amino acid into a formamide moiety. A reaction of such sort would lead to the generation of a novel class of formamides as shown in Figure 2. These form a new type of synthons to carry out the chemical transformations analogous to the existing reactions of the *N*-formyl group but over the C terminus of N^{α}-protected amino acids/peptide acids. Retrosynthetic analysis of the target formamide leads to a reaction of monoprotected *N*-Fmoc alkyl *gem*-diamine with a suitable existing formylating agent. But, since such a *gem*-diamine synthon is neither stable under acidic or

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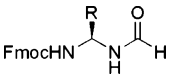
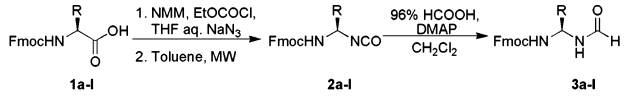


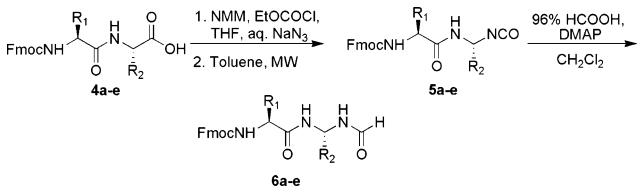
FIGURE 2. *N*-(1-(Fmoc amino)alkyl) formamide.

SCHEME 1. Synthesis of *N*-Fmoc α-Amino Acid Derived *N*-Formamides



R= H, CH_3, $CH_2C_6H_5$, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH_2CH_2SCH_3$, L-C_6H_5, D-C_6H_5, CH_2COOMe, $CH_2SCH_2C_6H_5$, -$(CH_2)_3$-

SCHEME 2. Conversion of *N*-Fmoc Peptide Acids into Formamides



6a: R_1 =R_2= $CH(CH_3)_2$; **6b**: R_1 = CH_3, R_2= $CH(CH_3)_2$; **6c**: R_1 = L-C_6H_5, R_2= CH_3; **6d**: R_1 = D-C_6H_5, R_2= CH_3; **6e**: R_1 = $CH(CH_3)_2$, R_2= D-$CH_2C_6H_5$

alkaline conditions[25] nor can be easily isolated,[26] this approach offers its own difficulties. Hence we envisaged an alternate route of employing stable *N*-Fmoc α-amino isocyanates as starting materials and directly formylating them under Goldsmith−Wick-type conditions.[27] Accordingly, we herein report a simple and efficient protocol for the conversion of *N*-Fmoc α-amino acids/peptide acids to the *N*-Fmoc α-amino formamides through the formolysis of the corresponding isocyanates (Scheme 1). The reaction is also an example for the transformation of the carboxylic acid group into the *N*-formyl functionality.

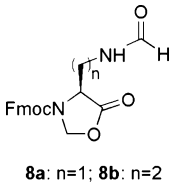
Our group has recently reported the preparation of *N*-Fmoc α-amino isocyanates and their application to the synthesis of dipeptidylureas[28] and oligo α-peptidyl ureas.[29] In another recent report, Guichard and co-workers also have employed the succinimidyl carbamate derivatives of *N*-Boc/Z/Fmoc protected α-amino acids in the synthesis of ureidopeptides and urea-peptide hybrids.[30] In the persistence of our efforts to explore newer applications of *N*-Fmoc α-amino isocyanates, we carried out the acidolysis reaction of the isocyanates with formic acid in the presence of 4-(dimethylamino)pyridine (DMAP) leading to the formation of the title formamides.

Studies on the reaction were initiated with Fmoc-phenylalanine **1c** as starting material. The required isocyanate precursor was prepared as an isolable solid through the Curtius rearrangement of the corresponding acid azide.[31,32] The isocyanate **2c** was then treated with nearly twice an equivalent of 96% formic acid with CH_2Cl_2 as solvent at −10 °C to yield the formamide **3c**. The reaction was run in both the absence and the presence of DMAP. As expected, there was a tremendous surge up to 90% in the yield for catalyzed reaction as against the uncatalyzed one. This observation was consistent with the proven mechanism of activation of isocyanates toward nucleophillic attack upon complexation with DMAP.[27] Parallel reactions were also run with other tertiary amino bases like *N*-methylmorpholine (NMM), pyridine, and triethylamine (TEA) as replacements to DMAP. But the yields in these cases were only up to 30−40% even with higher equivalents of base and longer reaction times (Table 1). The overall course of the DMAP-catalyzed formylation reaction starting from the corresponding isocyanate was complete within 2−3 h.

Also, the elevation in reaction temperature from −10 to 25 °C produced unsatisfactory yields with mixture of impurities. After having optimized the reaction conditions, the reaction was repeated for other *N*-Fmoc α-amino acids and in all the cases, corresponding *N*-formyl compounds **3a**−***l*** were obtained in good yields. Further, the extrusion of the products from the reaction mixtures as stable solids allowed for a simple workup procedure and product isolation with near purity. Final purification was done through recrystallization with the DMSO−water system.

TABLE 1. Yield of *N*-Fmoc-*g*Phe-CO-H over Different Bases

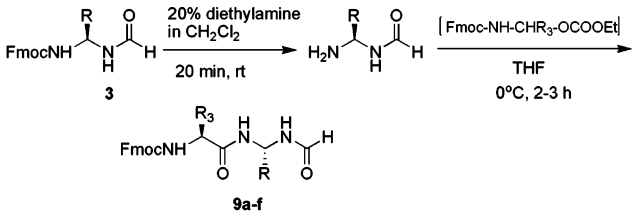
entry	base	reaction time (h)	equiv added	yield (%)
1	NMM	10	1.0	35
			2.0	45
2	pyridine	10	1.0	45
3	TEA	10	1.0	30
4	DMAP	4	1.0	85
		4	0.5	84
		4	0.3	84
		4	0.2	70



8a: n=1; **8b**: n=2

FIGURE 3. Formamides of N^{α}-Fmoc-Asp/Glu-5-oxazolidinone.

SCHEME 3. Synthesis of *N*-(1-Amino alkyl)formamides and Their Acylation



9a: R=H, R_3= $CH_2CH(CH_3)_2$; **9b**: R= $CH(CH_3)_2$, R_3= $CH_2CH_2SCH_3$; **9c:** R= $CH_2CH(CH_3)_2$, R_3= $CH(CH_3)_2$; **9d**: R= CH_3, R_3= $CH_2CH_2SCH_3$; **9e**: R= $CH(CH_3)CH_2CH_3$, R_3= $CH(CH_3)_2$; **9f**: R= $CH_2C_6H_5$, R_3= $CH_2CH(CH_3)_2$

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(32) The isocyanates were prepared either by refluxing the *N*-Fmoc α-amino acid azides in toluene for 30 min or by exposing the toluene solution of azides to microwave irradiation for 45 s at 600 MHz power. For experimental details and properties of these isocyanates see ref 28.

TABLE 2. List of Formamides Derived from *N*-Fmoc α-Amino Acids/peptide Acids

entry	formamides[b]	yield[a] (%)	mp (°C)	HRMS (M + Na^+) calcd	HRMS (M + Na^+) obsd
1	Fmoc-*g*Gly-CO-H **3a**	79	168	319.1059	319.1058
2	Fmoc-*g*Ala-CO-H **3b**	90	178	333.1215	333.1211
3	Fmoc-*g*Phe-CO-H **3c**	89	192	409.1528	409.1512
4	Fmoc-*g*Val-CO-H **3d**	89	183	361.1528	361.1526
5	Fmoc-*g*Leu-CO-H **3e**	86	156	375.1685	375.1687
6	Fmoc-*g*Ile-CO-H **3f**	80	140	375.1685	375.1686
7	Fmoc-*g*Met-CO-H **3g**	79	165	393.1249	393.1233
8	Fmoc-L-*g*Phg-CO-H **3h**	82	186	395.1372	395.1368
9	Fmoc-D-*g*Phg-CO-H **3i**	83	185	395.1372	395.1368
10	Fmoc-*g*Asp(OMe)-CO-H **3j**	78	138	391.1270	391.1266
11	Fmoc-*g*Cys(Bn)-CO-H **3k**	82	174	455.1405	455.1402
12	Fmoc-*g*Pro-CO-H ***3l***	75	gum	359.1372	359.1370
13	Fmoc-Val-*g*Val-CO-H **6a**	86	93	460.2212	460.2207
14	Fmoc-Ala-*g*Val-CO-H **6b**	82	210	432.1899	432.1895
15	Fmoc-L-Phg-*g*Ala-CO-H **6c**	83	183	466.1743	466.1737
16	Fmoc-D-Phg-*g*Ala -CO-H **6d**	80	179	466.1743	466.1737
17	Fmoc-Val-D-*g*Phe-CO-H **6e**	79	150	508.2212	508.2207
18	Fmoc-Phe-Ala-*g*Leu-CO-H **7**	78	152	593.2740	593.2733
19	Fmoc-Asp(β-NH-CHO)-5-oxazolidinone **8a**	81	152	389.1113	389.1108
20	Fmoc-Glu(γ-NH-CHO)-5-oxazolidinone **8b**	79	157	403.1270	403.1265

[a] Yields correspond to isolated formamides starting from isocyanates. [b] The "*g*" notation in Fmoc-gXaa-CO-H represents the *gem*-diamine derivative (see ref 30).

The generality of the reaction was demonstrated by the synthesis of Fmoc-protected di- and tripeptide acid derived *N*-formamides (Scheme 2). The required isocyanates were prepared through the rearrangement of the corresponding *N*-Fmoc dipeptide and tripeptide acid azides and reacted with 96% formic acid under similar reaction conditions to obtain the formamides **6a**−**e** and **7** in 78−86% yield and were fully characterized.

Finally the reaction was extended to the conversion of the side chain carboxylic acid of *N*-Fmoc-Asp/Glu derived 5-oxazolidinones into the *N*-formyl derivatives **(**Figure 3, **8a** and **8b**). In these preparations, the required products were isolated in 80% yield but the product isolation required workup procedures and column purification.

Although mild conditions were maintained throughout the reaction, the optical purity of the formamide products was verified by conducting studies using ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of both MPLC purified Fmoc-D-Phg-L-*g*Ala-CO-H and Fmoc-L-Phg-L-*g*Ala-CO-H showed distinct methyl group doublets at δ 1.16, 1.18 and δ 1.25, 1.26, respectively, while the mixture of epimers had two doublets at δ1.17, 1.18 and δ 1.24, 1.28. This clearly showed the absence of the formation of the other isomer due to epimerization during the reaction course.

We then undertook the deprotection of the Fmoc group form the *N*-formamides **3** to demonstrate their application in the synthesis of Fmoc-protected dipepidylformamides. Deprotection was carried out by stirring **3** in 20% diethylamine in CH_2Cl_2 solution for 20 min until the completion of the reaction as evident by TLC. The resulting amine-free *N*-(1-amino alkyl)-formamides were coupled directly with the mixed anhydride of Fmoc-amino acid to obtain Fmoc-dipeptidyl *N*-formamides **6d** and **9a**−**f** (Scheme 3, Table 3). All the peptide formamides thus prepared were adequately characterized.

In conclusion, we have synthesized a novel class of *N*-(1-Fmoc-amino alkyl)formamides employing the isocyanates derived from *N*-Fmoc α-amino acids/peptides. The formolysis reaction of the isocyanates has yielded the title compounds in excellent yields. The protocol has been extended to Fmoc dipeptides and tripeptides and also to the insertion of the *N*-formyl group in the side chains of Fmoc-Asp/Glu-derived 5-oxazolidinones. The reaction is simple, mild, high yielding, and racemization free.

TABLE 3. List of *N*-Fmoc-Dipeptidyl *N*-Formamides Synthesized via Scheme 3

compd	yield[a] (%)	mp (°C)	HRMS (M + Na)$^+$ calcd	HRMS (M + Na)$^+$ obsd
9a	79	128	432.1899	432.1890
9b	78	190	492.1933	492.1923
9c	83	192	474.2369	474.2367
9d	71	203	464.1620	464.1628
9e	77	217	474.2369	474.2366
9f	74	137	522.2369	522.2364

[a] Isolated yield from **3**.

Experimental Section

Typical Procedure for the Synthesis of *N*-Formamides. To a stirred solution of Fmoc-α amino acid/peptide acid (10 mmol) in THF were added 1.2 mL (11.0 mmol) of *N*-methylmorpholine and 1.05 mL (11.0 mmol) of ethyl chloroformate at −20 °C. The mixture was stirred for 5 min and 0.98 g (15 mmol) of sodium azide in a minimum amount of water was added. The stirring was continued for 20 min or until completion of the reaction. THF was then evaporated under vacuum and the residue was dissolved in CH_2Cl_2. The organic extract was washed with 5% Na_2CO_3, 10% citric acid, water, and brine and dried over anhydrous sodium sulfate. CH_2Cl_2 was removed under reduced pressure and the residue dissolved in 15.0 mL of toluene. The solution was refluxed for 30 min or irradiated with microwaves for 45 s at 600 MHz power. Complete conversion of acid azide (IR peak at 2145 cm^{-1}) to isocyanate (IR peak at 2225 cm^{-1}) was confirmed and toluene was removed in vacuo. The resulting isocyanate was dissolved in 15 mL of dry CH_2Cl_2. To this solution was added 0.79 mL of 96% formic acid (2.0 mmol) and 0.37 g of DMAP (0.3 mmol) at −10 °C with stirring for 4 h when a white precipitate appears. The solvent was evaporated, hexane was added, and the resulting solid was filtered. The solid product was washed with 10% citric acid (20 mL), 5% Na_2CO_3 (20 mL), and water and recrystallized with the DMSO−water system.

(*S*)-(9*H*-Fluren-9-yl)methyl 1-formamido-2-phenylethylcarbamate (Fmoc-*g*Phe-CO-H, 3c): yield 3.09 g (8.02 mmol, 80%) of white solid; mp 192 °C; R_f (10% MeOH/$CHCl_3$) 0.33; $[\alpha]^{24}_D$ 3.36 (*c* 1.1, DMSO); ^{1}H NMR (d_6-DMSO) δ 2.91 (br, 2H), 4.18 (br, m, 1H), 4.30 (d, J = 7.6 Hz, 2H), 5.11 (d, J = 6.8 Hz, 2H), 5.49 (d, J = 6.6 Hz, 1H), 7.07−7.31 (m, 7H), 7.37−7.48 (t, J = 14.1 Hz, 2H), 7.58 (d, J = 6.7 Hz, 2H), 7.72 (d, J = 7.1 Hz, 2H), 8.01 (d, J = 3.4 Hz, 1H), 8.12 (br, 1H); ^{13}C NMR (d_6-DMSO) δ 37.3, 47.2, 54.5, 66.5, 120.0, 124.8, 126.8, 127.1, 127.7, 127.9, 128.5, 129.4, 137.6, 141.5, 144.1, 156.6, 164.2.

(*S*)-(9*H*-Fluoren-9-yl)methyl 4-(2-formamidoethyl)-5-oxooxazolidine-3-carboxylate (Fmoc-Glu (γ-NHCHO)-oxazolidinone, 8b): yield: 2.67 g (7.12 mmol, 71%) of white solid; mp 157 °C; R_f (10% MeOH/$CHCl_3$) 0.31; $[\alpha]^{24}_D$ 75.6 (*c* 1.2, DMSO); ^{1}H NMR (d_6-DMSO) δ 1.84 (m, 2H), 3.31 (m, 2H), 4.21−4.34 (m, 3H), 4.71 (t, J = 12.9 Hz, 1H), 5.72 (s, 2H), 7.30−7.43 (m, 4H), 7.71−7.89 (m, 4H), 8.01 (m, 1H), 8.17 (s, 1H); ^{13}C NMR (d_6-DMSO) δ 26.2, 46.2, 46.5, 59.5, 65.4, 71.2, 119.8, 124.0, 127.0, 127.5, 141.0, 144.0, 160.0, 163.4, 168.0.

General Procedure for the Deprotection of the Fmoc Group from 3 and Acylation to Fmoc-Protected Peptidyl *N*-Formamides 9. To 18 mL of 20% diethylamine in CH_2Cl_2 was added *N*-Fmoc-amino-*N*-formamide **3** (1 mmol) and the mixture was stirred for 20 min at rt. After completion of the reaction (TLC), the solvent and an excess of diethylamine were removed completely under reduced pressure. The resulting *N*-(1-amino alkyl)formamide was dissolved in dry THF (5.0 mL) and maintained at 0 °C. To this was added the THF solution containing 1.1 mmol of Fmoc amino acid mixed anhydride and the resulting mixture was stirred for 2−3 h until completion of the coupling. The reaction mixture was then evaporated and triturated with water and ether. The solid product obtained was filtered, washed with aqueous 5% Na_2CO_3 (10 mL), 5% citric acid (10 mL), and water, dried, and recrystallized with DMSO−water.

(9*H*-Fluoren-9-yl)methyl 1-(1-formamido-3-methylbutylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (Fmoc-Phe-*g*Leu-CO-H, 9f): yield 3.60 g (7.21 mmol, 72%) of off-white solid; mp 137 °C; R_f (10% MeOH/$CHCl_3$) 0.27; $[\alpha]^{24}_D$ 9.00 (*c* 1.0, DMSO); ^{1}H NMR (d_6-DMSO) δ 0.95 (d, J = 5.6 Hz, 6H), 1.52 (m, 3H), 3.01 (m, 2H), 4.11 (t, J = 11.3 Hz, 1H), 4.24 (d, J = 7.2 Hz, 2H), 4.51 (m, 1H), 5.32 (m, 1H), 6.12 (m, 1H), 7.10−7.90 (m, 13H), 8.12 (m, 1H), 8.24 (m, 1H); ^{13}C NMR (d_6-DMSO) δ 21.6, 25.3, 37.3, 46.7, 46.9, 51.3, 61.8, 65.7, 119.9, 125.3, 126.2, 127.2, 127.3, 127.6, 128.8, 130.4, 132.3, 138.1, 140.6, 143.7, 155.6, 164.1, 173.9.

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Supporting Information Available: Characterization data of all the compounds, ^{1}H NMR spectra of compounds **3c**,**f**,**g**,**j**, **6a**,**c**,**d**, and **7**, ^{13}C NMR spectra of the compounds **3b**,**d**,**f**,**g**,**j** and **7**, HRMS of **3a**−**e**,**g**,**h**,**j**, **6a**,**c**,**e**, **7**, **8b**, and **9b**,**c**, LCMS of **3a**,**d**,***l*** and **8a**, ESMS of **3e**, **6b**,**c**, and **8b**, and MALDITOF of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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