ORGANIC LETTERS

2011
Vol. 13, No. 15
3952–3955

A Remarkably Simple Protocol for the *N*-Formylation of Amino Acid Esters and Primary Amines

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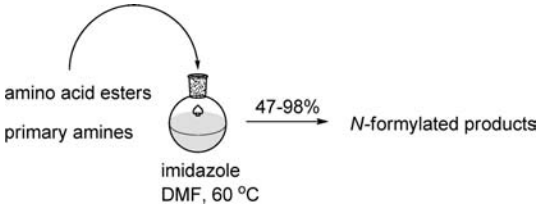
Received May 31, 2011

ABSTRACT



A simple, convenient, and wide scope protocol for the *N*-formylation of amino acid esters and primary amines has been developed utilizing only imidazole in warm DMF.

The protection of reactive amino groups is very commonly required in organic synthesis. The formyl (CHO) group may be used for this purpose, and numerous methods are available for the formylation of amines and amino acids.[1] *N*-Formylated amino acid esters have been utilized for peptide synthesis[2] and may also serve as precursors of isocyanides, which find use in multicomponent reactions to furnish a wide variety of products.[3]

Many of the currently available methods for the *N*-formylation of amino acid derivatives require harsh reaction conditions resulting in tedious purification[1f,k] (e.g., triethylorthoformate at 140 °C followed by vacuum distillation) and use of toxic[1g] (e.g., cyanomethylformate) or somewhat unstable reagents (e.g., pentafluorophenyl formate).[1c,e] In addition, some reagents require the reaction to be performed under an inert atmosphere using rigorously dried solvents.[1d,h]

Herein, we report an alternative method for the *N*-formylation of amino acid esters based on treatment with imidazole in warm (60 °C) DMF. The reagents used are inexpensive and neither inert atmosphere nor dry solvent are required for the reaction to proceed. Moreover, the reaction work up and purification of the products is straightforward and provides the corresponding *N*-formylated amino acid esters in good yields (47−79%). We also present evidence that DMF is the formyl donor and that an acyl transfer agent, preferably imidazole, is required rather than just an organic base. This method does not require additional reagents, such as chlorotrimethylsilane, to activate the DMF.[1d]

During the course of other studies in our laboratory, we wished to prepare a 1-Me-histidine (1-Me-His-OH). The synthesis of 1-Me-His-OH (in 3 steps from **1a**) has been described by Jain and Cohen,[4a] and involves the reaction of His-OMe·2HCl (**1a**) with carbonyldiimidazole (CDI) in DMF as an initial step. A cyclic urea **3** (Scheme 1) is

(1) For the review on acylating agents, see: (a) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671. For selected examples of *N*-formylating agents, see:(b) Martinez, J.; Laur, J. *Synthesis* **1982**, 979. (c) Kisfaludy, L.; Ötvös, L., Jr. *Synthesis* **1987**, 510. (d) Berry, M. B.; Blagg, J.; Craig, D.; Willis, M. C. *Synlett* **1992**, 659. (e) Akikusa, N.; Mitsui, K.; Sakamoto, T.; Kikugawa, Y. *Synthesis* **1992**, 1058. (f) Chancellor, T.; Morton, C. *Synthesis* **1994**, 1023. (g) Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H. J. *Synthesis* **1996**, 37. (h) Giard, T.; Bénard, D.; Plaquevent, J. C. *Synthesis* **1998**, 297. (i) Meinnel, T.; Patiny, L.; Ragusa, S.; Blanquet, S. *Biochemistry* **1999**, *38*, 4287. (j) Yang, D.; Jeon, H. B. *Bull. Korean Chem. Soc.* **2010**, *31*, 1424. (k) Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2010**, *51*, 4186.

(2) For selected examples see: (a) Sheehan, J. C.; Yang, D. D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1154. (b) Boulay, F.; Tardiff, M.; Brouchon, L.; Vignais, P. *Biochem. Biophy. Res. Commun.* **1990**, *168*, 1103. (c) Stephenson, K. A.; Zubieta, J.; Banerjee, S. R.; Levadala, M. K.; Taggart, L.; Ryan, L.; McFarlane, N.; Boreham, D. R.; Maresca, K. P.; Babich, J. W.; Valliant, J. F. *Bioconjugate Chem.* **2004**, *15*, 128.

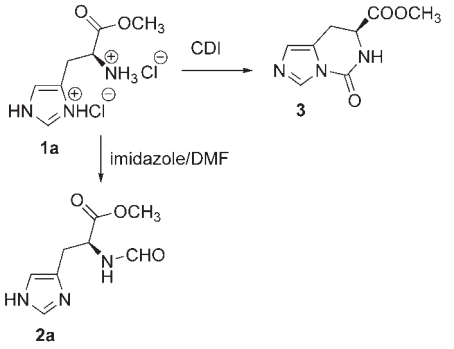
(3) For the recent review on Ugi multicomponent reaction, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. For selected examples, see:(b) Urban, R.; Marquarding, D.; Seidel, P.; Ugi, I.; Weinelt, A. *Chem. Ber.* **1976**, *110*, 2012. (c) Mayer, J.; Umkehrer, M.; Kalinski, C.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2005**, *46*, 7393.

(4) (a) Jain, R.; Cohen, L. A. *Tetrahedron* **1996**, *52*, 5363. (b) Guillen, F.; Brégeon, D.; Plaquevent, J. C. *Tetrahedron Lett.* **2006**, *47*, 1245.

10.1021/ol201475j
Published on Web 06/28/2011

formed during this step, which is subsequently transformed to 1-Me-His-OH.[4a] Initial attempts to repeat the synthesis of **3** failed. As indicated in their work,[4a] crude product **3** was expected to crystallize after a standard extractive workup. In our hands, no crystallization occurred despite many attempts and the product was ultimately obtained by flash column chromatography (FCC) (see Supporting Information). Analysis of the compound by ^{1}H NMR revealed the presence of additional signals (δ 11.87, s, D_2O exch., 1H) and (δ 8.01, s, 1H), which were not consistent with the structure of cyclic urea **3**. The signal at 8.01 ppm suggested the presence of a formyl group; this hypothesis was further supported by the presence of the signal at δ 161.2 ppm in ^{13}C NMR spectrum (DMSO−D_6). The unknown product was assigned the structure of *N*-formyl His-OMe (**2a**, Scheme 1);[5] a proposal consistent with the high resolution mass spectral data (HRMS) obtained.

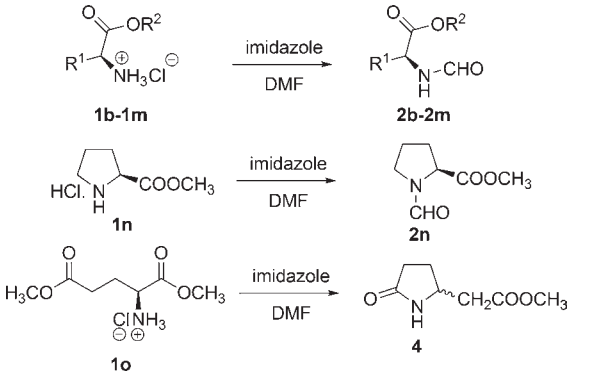
Scheme 1. Reaction of **1a** with CDI and Imidazole/DMF



The unexpected formation of *N*-formyl His-OMe (**2a**) prompted us to investigate the quality of reagents used in the reaction which revealed that the CDI had completely hydrolyzed to imidazole (^{1}H NMR inspection) during prolonged storage. When **1a** was treated with "genuine" imidazole, *N*-formyl His-OMe (**2a**) was isolated as a sole product in 51% yield. It is worth noting, that successful transformation of **1a** to the cyclic urea **3** was achieved using fresh CDI and the procedure described by Guillen et al.[4b] which afforded better yields than Jain and Cohen procedure.[4a]

The observed formation of **2a** suggested that DMF in the presence of imidazole, without any additional reagents, acts as an acylating agent for the synthesis of *N*-formyl amino acid derivatives. To investigate the scope of this reaction, a variety of amino acid esters were screened. The results of these studies are depicted in Scheme 2 and summarized in Table 1. When Phe-OEt · HCl (**1b**) was treated with imidazole in warm (60 °C) DMF, *N*-formyl Phe-OEt (**2b**, Scheme 2) was isolated in 79% yield. Unfortunately treatment of phenylalanine (Phe-OH) under the same conditions only afforded an intractable mixture of products, suggesting, that amino acids need to be protected as esters in order to achieve the *N*-formylation. The protecting groups present in amino acid esters **1c**, **1g**, **1h** and **1l** are retained in the corresponding *N*-formyl derivatives **2c**, **2g**, **2h** and **2l**. The corresponding *N*-formyl derivatives **2b**−**2n** were obtained in moderate to good yields (47−79%, Table 1) and were characterized by ^{1}H NMR, ^{13}C NMR and HRMS (see Table 1 and SI).[6] The reactions were performed at 1 mmol scale (2 eq of imidazole, 60 °C, 48 h). The *N*-formylation of Phe-OEt · HCl (**1b**) was also performed at 10 mmol scale (see SI for details), providing **2b** in 55% yield indicating scalability of the method. Importantly, no racemization was observed during the reaction as indicated by the comparison of $[\alpha]_D$ values for compounds **2b**, **2d**, **2f** and **2i** with those available in the literature (Table 1).

Scheme 2. *N*-Formylation of Amino Acids **1a**−**1n** and Formation of **4**



One noticeable exception was found when Glu(OMe)-OMe (**1o**) was subjected to the reaction conditions; no product of *N*-formylation was obtained. Instead, the partially racemized lactam **4** (Table 1) was isolated in 30%

(5) We were unable to compare the spectral data obtained for **2a** with the literature. There is only one reference describing the use of **2a** for the preparation of polymeric polyoxyethylene catalysts, however neither the procedure for the preparation nor the spectral data are provided, see: Topicheva, I. N.; Solovieva, A. B.; Kabanov, V. A. *Dokl. Akad. Nauk SSSR* **1971**, *199*, 1084.

(6) Due to the restricted rotation, the presence of two rotamers was consistently observed in the NMR spectra acquired in $CDCl_3$. Although the amount of minor rotamer is small (< 5%) in most of the cases, it is more prevalent in the case of *N*-formyl Ile-OMe (**2i**, ca. 10%) and *N*-formyl Pro-OMe (**2n**, ca. 40%).

(7) Amere, M.; Lasne, M. C.; Rouden, J. *Org. Lett.* **2007**, *9*, 2621.

(8) Only the optical rotation of unnatural *R* enantiomer of **2d** has been determined, see: Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196.

(9) (a) Andersen, T. P.; Ghattas, A. B. A. G.; Lawesson, S. O. *Tetrahedron* **1983**, *39*, 3419. (b) Anderson, W. K.; Bhattacharjee, D.; Houston, D. M. *J. Med. Chem.* **1989**, *32*, 119.

(10) Note that the values for the optical rotation reported for *N*-formyl Ile-OMe (**2i**) in Aitali, M.; Allaoud, S.; Karim, A.; Mortreux, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1367 and in ref 1h have opposite signs (Table 1). Our value (Table 1) indicates that **2i** is dextrorotatory.

(11) (a) Cappon, J. J.; van der Walle, G. A. M.; Verdegem, P. J. E.; Raap, J.; Lugtenburg, J. *Rec. Trav. Chim. Pays-Bas* **1992**, *111*, 517. (b) Hinderaker, M. P.; Raines, R. T. *Protein Sci.* **2003**, *12*, 1188.

Table 1. *N*-Formylation of Amino Acid Esters **1a**–**1o**, Selected Data

	R^1 (amino acid)	R^2	yield (%)	$[\alpha]_D$	δ CHO $^1H/^{13}C$ (ppm)[a]
1a→2a	His	Me	51	+20.1 (c 1, MeOH)	8.01/161.2 (DMSO–D_6)
1b→2b	Phe	Et	79	+72.7 (c 0.55, CH_2Cl_2) +81.7 (c 1.78, $CHCl_3$)[1g] +76.0 (c 0.55, $CHCl_3$)[7]	8.17/160.4 ($CDCl_3$), see ref 7
1c→2c	Tyr(*t*-Bu)	Me	73	+57.5 (c 1, $CHCl_3$)	8.14/160.4 ($CDCl_3$)
1d→2d	Trp	Me	48	+52.1 (c 1.1, $CHCl_3$) –51.8 (c 1.1, $CHCl_3$)[8]	8.12/160.7 ($CDCl_3$), see refs 1k, 8
1e→2e	Gly	Et	55	optically inactive	8.24/160.9 ($CDCl_3$), see ref 9
1f→2f	Ala	Me	53	–61.8 (c 0.6, EtOH) –34.7 (c 0.6, EtOH)[1g] –34.6 (c 0.6, EtOH)[1h]	8.17/160.3 ($CDCl_3$), see ref 1h
1 g→2 g	Ser(*t*-Bu)	Me	67	+13.4 (c 1, $CHCl_3$)	8.22/160.7 ($CDCl_3$)
1 h→2 h	Cys(Bn)	Me	47	+6.1 (c 1, $CHCl_3$)	8.10/160.5 ($CDCl_3$)
1i→2i	Ile	Me	62	+27.6 (c 1, $CHCl_3$) +32.5 (c 1, $CHCl_3$)[10] –32.3 (c 1, $CHCl_3$)[1h]	8.26^{ma} $7.99^{mi}/163.6^{mi}160.6^{ma}$ ($CDCl_3$),see refs 1h, 10
1j→2j	Met	Me	59	+38.8 (c 1, $CHCl_3$)	8.21/160.7 ($CDCl_3$)see ref 1i
1k→2k	Asp(OMe)	Me	50	+12.3 (c 1, $CHCl_3$)	8.18/160.7 ($CDCl_3$)
1 L→2 L	Lys(Boc)	Me	69	+12.6 (c 1, $CHCl_3$)	8.19/160.8 ($CDCl_3$)
1 m→2 m	Arg(NO_2)	Me	56	–1.2 (c 0.4, MeOH)	8.06/161.1 (DMSO–D_6)
1n→2n	Pro	Me	76	–89.5 (c 1, $CHCl_3$)	8.26^{ma} $8.23^{mi}/161.5^{mi}160.7^{ma}$($CDCl_3$), see ref 11
1o→4	Glu(OMe)	Me	30	+3.6 (c 1, EtOH) +10.5 (c 1, EtOH)	no CHO group in **4**

[a] ma, major rotamer; mi, minor rotamer.

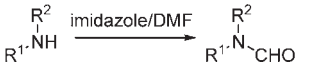
yield after FCC.[12] No trace of *N*-formyl Glu(OMe)-OMe was detected (^1H NMR inspection).

With a general strategy for the *N*-formylation of amino acid esters established, we were interested in applying it to the *N*-formylation of amines (Scheme 3). Benzylamine (**5a**), aniline (**5b**) and *N*,*N*-dicyclohexylamine (**5c**) were selected as examples of primary aliphatic, primary aromatic and secondary amines. Treatment of **5a**–**c** under the previously established reaction conditions showed the reactions to be rather sluggish. Reaction of benzylamine (**5a**) resulted in an unacceptable yield (ca. 20%) of *N*-formyl benzylamine (**6a**) while a complete recovery of starting materials was observed for aniline (**5b**) and *N,N*-dicyclohexylamine (**5c**). When the temperature was increased to 120 °C, *N*-formyl benzylamine (**6a**) was isolated in excellent yield (98%, Scheme 3).[13] On the other hand, massive decomposition was observed when aniline (**5b**) and *N,N*-dicyclohexylamine (**5c**) were treated with imidazole in DMF at 140 °C. Only a trace amount (ca. 1%) of *N*-formylated product **6b**[13] was isolated from the reaction mixture (Scheme 3) after extractive workup and FCC, while no *N*-formyl-*N,N*-dicyclohexylamine (**6c**, Scheme 3) was isolated. The lack of reactivity is likely caused by decreased nucleophilicity of aromatic amine **5b** and steric hindrance of the secondary amine **5c**. It appears that the presented synthetic methodology can only be successfully extended to the *N*-formylation of primary amines (see SI for details).

(12) Jain, R. *Org. Prep. Proc. Int.* **2001**, *33*, 405.

(13) Spectral data of **6a** and **6b** were in agreement with those previously reported, see: Katritzky, A. R.; Chang, H. X.; Yang, B. *Synthesis* **1995**, 503.

Scheme 3. *N*-Formylation of Amines **5a**–**5c**



5a, R^1 = Bn, R^2 = H — **6a**, R^1 = Bn, R^2 = H
5b, R^1 = Ph, R^2 = H — **6b**, R^1 = Ph, R^2 = H
5c, $R^1 = R^2$ = cyclohexyl — **6c**, $R^1 = R^2$ = cyclohexyl

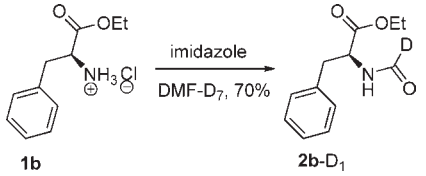
Several experiments with Phe-OEt·HCl (**1b**) were carried out in order to understand the mechanism of the reaction. First, the reaction was carried out in the absence of imidazole. The reaction did not proceed at all and no *N*-formyl Phe-OEt (**2b**) was detected (^1H NMR inspection). Replacement of imidazole with other organic bases (Et_2NH, Et_3N or piperidine) also resulted in a complete recovery of starting material, with no trace of **2b** detected. We therefore deduced that the presence of imidazole is required for the reaction to proceed.

It was also found, that 2 equiv of imidazole are required for the reaction to proceed within a reasonable period of time (48 h). Lowering the amount of imidazole slows the reaction, while increasing the amount of imidazole (>2 equiv) does not seem to have a significant impact on the rate of the reaction. Indeed, larger amounts of imidazole in several instances complicate the purification of final products **2**.

To establish the origin of the formyl (CHO) group in *N*-formyl Phe-OEt (**2b**), a formylation of Phe-OEt·HCl (**1b**)

was carried out in DMF-D_7 as a solvent (Scheme 4). The product of formylation **2b**-D_1 was obtained in 70% yield and was characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. In ^{1}H NMR spectrum, an absence of the signal at δ 8.17 ppm (CHO proton) was observed; on the other hand a presence of triplet at δ 160.3 ppm (CDO carbon) was observed in ^{13}C NMR spectrum (see SI). The mass spectrum (EI) was also consistent with the structure **2b**-D_1. These results indicate that the *N*-formyl group present in amino acid esters **2a**−**2n** and in formamides **6a** and **6b** originates from DMF, which is used as a solvent in these reactions.

Scheme 4. *N*-Formylation of Phe-OEt·HCl (**1b**) in DMF-D_7

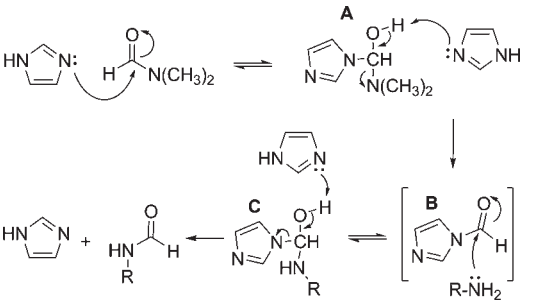


1b **2b**-D_1

A plausible mechanism for the *N*-formylation of amino acid esters and amines, consistent with the results of our experiments, is depicted in Scheme 5. Nucleophilic attack of imidazole on DMF results in the formation of a tetrahedral intermediate **A**. Collapse of **A** leads to the formation of the reactive *N*-formyl imidazole (intermediate **B**, Scheme 5). This intermediate has been previously postulated to act as an acyl transfer reagent in the *N*-formylation of amines by a mixture of formic acid, oxalyl chloride and imidazole.[14] Nucleophilic attack of the amino acid ester **1a**−**1n** or amine (**5a** and **5b**) on intermediate **B** gives a tetrahedral intermediate **C**, which collapses with the formation of *N*-formylated products **2a**−**2n**, **6a** and **6b**.

This mechanism suggests that other acyl transfer catalysts may also be compatible with the reaction. To this end, pyridine, 4-*N,N*-dimethylaminopyridine (DMAP) and *N*-methylimidazole were investigated in reaction with **1b**. None of these agents worked as well as imidazole under the same conditions (1 mmol scale, 60 °C, DMF). After 24 h of reaction, the reactions in the presence of pyridine or DMAP demostrated lower reactivity showing only 14 and 19% conversion (crude reaction mixture analyzed by ^{1}H NMR), respectively. *N*-Methylimidazole performed better with 37% isolated yield at 48 h, yet still fell short of the performance of imidazole (2b, 79%).

Scheme 5. Plausible Mechanism for the *N*-Formylation of Amino Acid Esters **1a**−**1n** and Amines **5a, 5b**



In summary, we have developed a simple protocol for the *N*-formylation of amino acid esters and primary amines. The major advantages of our approach are (i) the use of widely available and inexpensive reagents and (ii) experimentally simple protocol, requiring neither dry solvents nor an inert atmosphere. The described protocol could furnish *N*-formylated derivatives which are suitable for conversion into amino acid or amine-derived isocyanides, which themselves have synthetic use as substrates in the Ugi multicomponent reaction, for example.[15] As well, this work prompts us to make a cautionary note for reactions taking place in warm/hot DMF in the presence of nucleophilic acyl transfer catalysts as this may lead to unwanted formylated byproducts.

Acknowledgment. The financial support from The Ontario Institute for Cancer Research (OICR) is gratefully acknowledged. We thank Prof. J. M. Chong (University of Waterloo) for the assistance with optical rotation measurements.

Supporting Information Available. Complete experimental details, spectral characterization of compounds **2a**−**2n**, **4**, **6a** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Kitagawa, T.; Arita, J.; Nagahata, A. *Chem. Pharm. Bull.* **1994**, *42*, 1655. (b) Kitagawa, T.; Ito, J.; Tsutsui, C. *Chem. Pharm. Bull.* **1994**, *42*, 1931. Our attepmts to isolate or detect the presence of *N*-formyl imidazole in the reaction mixture containing no external nucleophile (**1a**−**1n** or **5a, 5b**) failed, presumably due to the termal instability of *N*-formyl imidazole.

(15) Recently there has been a growing interest in the use of Ugi multicomponent reaction as a key step in the formation of cyclen-derived ligands, suitable for the preparation of, for example, MRI contrast agents, see: (a) Main, M.; Snaith, J. S.; Meloni, M. M.; Jauregui, M.; Sykes, D.; Faulkner, S.; Kenwright, A. M. *Chem. Commun.* **2008**, 5212. (b) Piersanti, G.; Remi, F.; Fusi, V.; Formica, M.; Giorgi, L.; Zappia, G. *Org. Lett.* **2009**, *11*, 417. (c) Tei, L.; Gugliotta, G.; Avedano, S.; Giovenzana, G. B.; Botta, M. *Org. Biomol. Chem.* **2009**, *7*, 4406.