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Efficient Transamidation of Primary Carboxamides by in Situ Activation with *N*,*N*-Dialkylformamide Dimethyl Acetals

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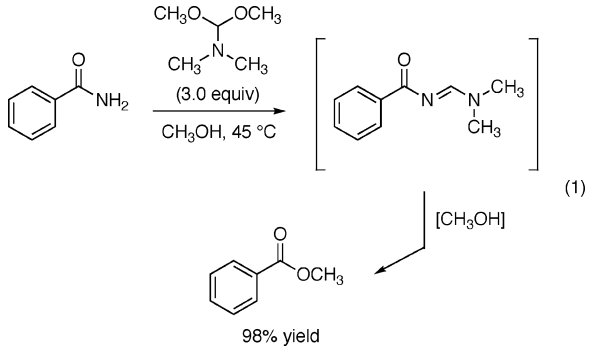
Abstract: Two protocols for the transamidation of primary amides with primary and secondary amines, forming secondary and tertiary amides, respectively, are described. Both processes employ *N*,*N*-dialkylformamide dimethyl acetals for primary amide activation, producing *N*′-acyl-*N*,*N*-dialkylformamidines as intermediates, as widely documented in the literature. Although the latter intermediates react irreversibly with amines by amidinyl transfer, we show that in the presence of certain Lewis acid additives efficient acyl transfer occurs, providing new and useful methods for amide exchange. In one protocol for transamidation, the *N*′-acyl-*N*,*N*-dialkylformamidine intermediates are purified by flash-column chromatography and the purified intermediates are then treated with an amine (typically, 2.5 equiv) in the presence of scandium triflate (10 mol %) in ether to form in high yields the products of transamidation. In a second procedure, *N*′-acyl-*N*,*N*-dialkylformamidines are generated in situ and, without isolation, are subjected to transamidation in the presence of zirconium chloride (0.5 equiv) and an amine (typically 2 equiv). A variety of different primary amides and amines are found to undergo efficient transamidation using the methods described.

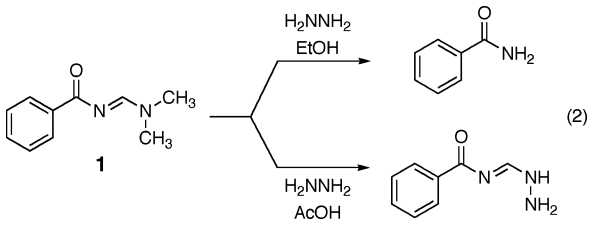
Introduction

In the context of a recent synthetic problem, we wished to transform a readily available primary carboxamide substrate into various secondary and tertiary amides. Existing methods to accomplish the desired amide exchange involved harsh reaction conditions,[1] required more than one step,[2] were limited in substrate scope,[3] or were reversible,[4] leading us to consider developing alternative chemistry. In this regard, the prior work of Anelli et al. was of particular interest, as these researchers had reported that primary carboxamides could be treated with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA)[5] in methanol at 45 °C to furnish methyl esters, via an *N*-acylformamidine intermediate (formed in situ, eq 1).[6] This transformation was



(1)

notable in that the *N*-acyl group had served as the site of nucleophilic addition, not the formamidinyl group, which is more typical. For example, Lin et al. have shown that the reaction of *N*′-benzoyl-*N*,*N*-dimethylformamidine (**1**) with hydrazine in ethanol forms benzamide, whereas in acetic acid amidinyl exchange occurs, but in both cases the amidinyl carbon atom is the site of nucleophilic addition (eq 2).[7a] We wondered



(2)

whether a nonsolvent nucleophile such as a primary or secondary amine might under appropriate conditions react with an *N*-acylformamidine intermediate by *N*-acyl transfer rather than

(1) (a) Galat, A.; Elion, G. *J. Am. Chem. Soc.* **1943**, *65*, 1566. (b) Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035. (c) Shi, M.; Cui, S.-C. *Synth. Commun.* **2005**, *35*, 2847.
(2) (a) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607. (b) Garcia, J.; González, J.; Segura, R.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1984**, *49*, 3322. (c) Davidsen, S. K.; May, P. D.; Summers, J. B. *J. Org. Chem.* **1991**, *56*, 5482.
(3) For transamidation of dimethylformamide, see: (a) Pettit, G. R.; Thomas, E. G. *J. Org. Chem.* **1959**, *24*, 895. (b) Pettit, G. R.; Kalnins, M. V.; Liu, T. M. H.; Thomas, E. G.; Parent, K. *J. Org. Chem.* **1961**, *26*, 2563. (c) Kraus, M. A. *Synthesis* **1973**, 361. Transamidation of *N*-hydroxyethyl α-amino amides: (d) Snuggs, J. W.; Pires, R. M. *Tetrahedron Lett.* **1997**, *38*, 2227. Transamidation of *N*-(carbamoylmethyl)-*N*′-tosylguanidines: (e) Lasri, J.; González-Rosende, M. E.; Sepúlveda-Arques, J. *Org. Lett.* **2003**, *5*, 3851. Transamidation of *N*-acyltrifluoromethanesulfonamides: (f) Guillard, S.; Aramini, A.; Cesta, M. C.; Colagioia, S.; Coniglio, S.; Genovese, F.; Nano, G.; Nuzzo, E.; Orlando, V.; Allegretti, M. *Tetrahedron* **2006**, *62*, 5608.
(4) (a) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422. (b) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *34*, 938.
(5) For a review of the chemistry of formamide acetals, see: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.
(6) Anelli, P. L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* **1997**, *38*, 2367.

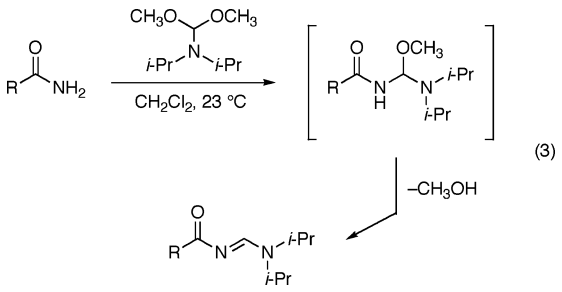
10.1021/ja066728i CCC: $33.50

formamidinyl transfer. Unlike the ester formation described by Anelli et al.,[6] the proposed amide formation would likely not have the advantage of reversibility if transfer of the formamidinyl group to the nucleophile occurred. Here, we show that *N*-acyl formamidines do indeed react irreversibly with amines by formamidinyl transfer in the absence of additives, but that in the presence of certain Lewis acids efficient acyl transfer occurs, providing useful processes for amide exchange.

Results and Discussion

The synthesis of *N*′-acyl-*N*,*N*-dimethylformamidines from primary amides and DMF-DMA is well precedented.[7] While there are several examples of reaction occurring at 23 °C,[7b−e] in other precedents the amidine formation is conducted at much higher temperatures.[7a,f−k] In our studies both aliphatic and aromatic primary amide substrates were typically transformed to the corresponding *N*,*N*-dimethylformamidine derivatives within 2−4 h upon exposure to DMF-DMA (1.3 equiv) in refluxing dichloromethane (∼0.1 M in substrate) containing crushed, activated 5 Å molecular sieves (100 mg/mL). The more hindered substrate pivalamide required 24 h for complete conversion under the same conditions. The transformations are readily monitored by thin-layer chromatography, and the products are stable to column chromatography (though we typically do not isolate them, vide infra). When isolated, *N*′-acyl-*N*,*N*-dimethylformamidines are often solids, and they are produced in near-quantitative yields, as previously documented.[7]

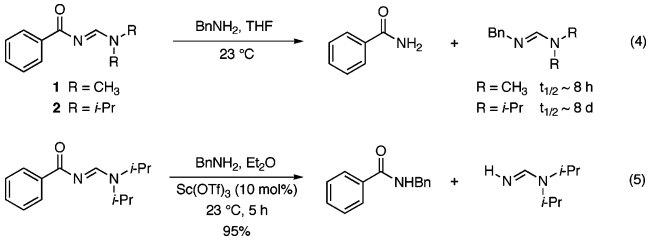
In addition to *N*′-acyl-*N*,*N*-dimethylformamidines, we prepared *N*′-acyl-*N*,*N*-diisopropylformamidines by the reaction of primary amides with *N*,*N*-diisopropylformamide dimethyl acetal (DIF-DMA, 1.25 equiv, eq 3). The latter reagent is not presently



(3)

available commercially, but it is readily prepared in quantity from *N*,*N*-diisopropylformamide.[8] The reactions of primary amides with DIF-DMA are much faster than those with DMF-DMA and typically proceed to completion within 2−4 h at 23 °C when conducted in the presence of crushed, activated 5 Å molecular sieves. Products formed in the absence of sieves contained ∼15% of an impurity believed to be the partially condensed orthoamide intermediate depicted in eq 3 (bracketed structure, on the basis of ^{1}H NMR analysis of crude reaction mixtures), a substance found to be a catalyst poison in one of the two transamidation protocols we report (vide infra). The impurity is largely transformed to the corresponding *N*′-acyl-*N*,*N*-diisopropylformamidine on silica gel, for isolated yields of the latter typically exceed 95% after flash-column chromatography. Crude products formed in the presence of 5 Å molecular sieves typically contain <3% of the orthoamide impurity. Like *N*′-acyl-*N*,*N*-dimethylformamidines, *N*′-acyl-*N*,*N*-diisopropylformamidines are typically solids, and as implied above, they are stable to chromatography. *N*′-Acyl-*N*,*N*-diisopropylformamidines are typically slightly less polar than the starting primary amides, whereas *N*′-acyl-*N*,*N*-dimethylformamidines are typically slightly more polar.

We first explored the reaction of chromatographically purified (>95%) *N*′-benzoyl-*N*,*N*-dimethylformamidine (**1**) with benzylamine (2 equiv) in the absence of any additive, in the aprotic solvent tetrahydrofuran (THF), and observed that nearly complete conversion to benzamide and *N*′-benzyl-*N*,*N*-dimethylformamidine occurred within 15 h at 23 °C (eq 4, R = CH_3). Thus, as Lin et al. had found using hydrazine as the nucleophile in protic media,[7a] amidinyl transfer proceeded to the exclusion of acyl transfer and was apparently irreversible. We attempted to alter the course of reaction by increasing the size of the amidinyl *N*-alkyl substituents, examining the reaction of *N*′-benzoyl-*N*,*N*-diisopropylformamidine (**2**) with benzylamine (2 equiv) in THF at 23 °C (eq 4, R = *i*-Pr). Although the rate of amidinyl transfer was indeed greatly slowed, this was nevertheless the primary course of reaction; after 4 d at 23 °C, ∼25% of the starting material had been transformed cleanly to benzamide. Lewis acid additives were found to dramatically alter the rate and course of reaction. From an initial screen of the influence of different Lewis acids upon the reaction of **1** with benzylamine, scandium triflate emerged as particularly efficacious.[9] In the presence of 10 mol % scandium triflate and 3 equiv of benzylamine in THF a 5:1 mixture of *N*-benzylbenzamide, the product of acyl transfer, and benzamide, the product of amidinyl transfer, respectively, was formed within 2 h at 23 °C. Amidinyl transfer



was completely suppressed when **2** was used as the substrate, in an otherwise identical transformation, but the reaction required 3 d to achieve complete conversion at 23 °C. Use of ether as the solvent rather than THF led to a significant increase in the rate of the latter reaction, and a high selectivity for acyl transfer was maintained. Thus, treatment of **2** with benzylamine

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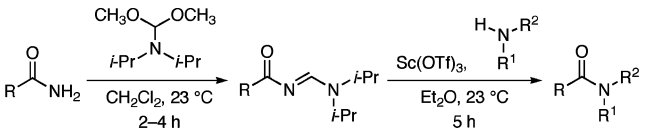
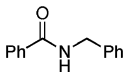
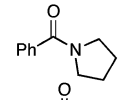
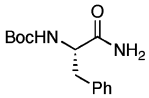
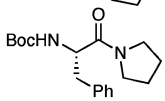
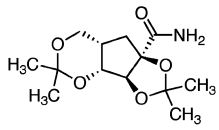
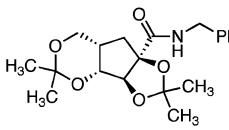
(8) Bredereck, H.; Simchem, G.; Rebsdat, S.; Kantlehn, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshab, P. *Chem. Ber.* **1968**, *101*, 41.

(9) Titanium isopropoxide, titanium tetra(dimethylamide), tris(dimethylamido)-aluminum(III) dimer, ytterbium triflate, and zinc chloride were ineffective or were substantially less active than scandium triflate in promoting the transamidation of *N*,*N*-dialkyl-*N*′-acylformamidines with benzylamine as the nucleophile at 23 °C.

Table 1. Transamidation Using DIF-DMA as the Activator and Scandium Triflate as the Lewis Acid Additive, Representative Examples[a]



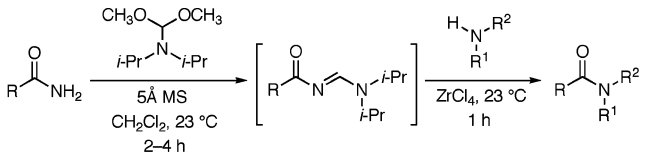
Entry	Substrate	Amine	Product	Yield
1				92%
2				92%
3				90%
4				97%

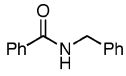
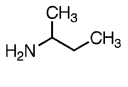
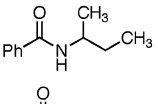
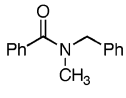
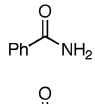
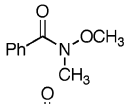
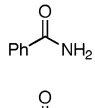
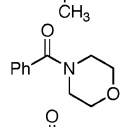
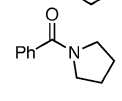
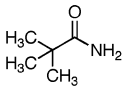
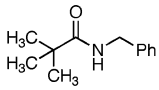
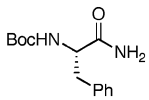
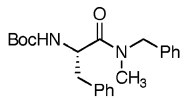
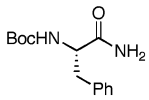
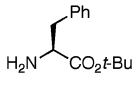
[a] Reactions employed 2.5 equiv of amine and 10 mol % scandium triflate. Reported yields are for chromatographically purified products of the two-step sequence shown.

(2 equiv) in the presence of scandium triflate (10 mol %) in ether at 23 °C for 5 h afforded *N*-benzylbenzamide in 95% yield after aqueous workup and flash-column chromatography (eq 5). These conditions proved to be effective for other transamidations as well, as illustrated by the representative examples shown in Table 1. Briefly, both aliphatic and aromatic *N*′-acyl-*N*,*N*-diisopropylformamidines proved to be viable substrates, but with the exception of pyrrolidine, only primary amines were effective as nucleophiles. In a series of control experiments (not detailed), we established that the partially condensed orthoamide intermediate discussed above (the bracketed structure in eq 3) served as a catalyst poison, necessitating that the *N*′-acyl-*N*,*N*-diisopropylformamidine intermediates be purified by flash-column chromatography prior to the transamidation. This requirement effectively made the method described a two-step process, albeit one of high efficiency.

A one-flask procedure for transamidation, not requiring chromatographic purification of the *N*′-acyl-*N*,*N*-dialkylformamidine intermediate, was also developed. This procedure employs 1/2 equiv of zirconium chloride as the Lewis acid additive (stored and dispensed as a 0.7 M solution in acetonitrile) and is effective with both *N*′-acyl-*N*,*N*-diisopropylformamidines and *N*′-acyl-*N*,*N*-dimethylformamidines as substrates. In this transamidation procedure, a primary carboxamide substrate is first activated with DIF-DMA or DMF-DMA (in the presence of 5 Å molecular sieves, as described above) and the *N*′-acyl-*N*,*N*-dialkylformamidine intermediate that is formed—without isolation—is treated sequentially with 2−3 equiv of an amine and 0.5 equiv of zirconium chloride. Transamidations are typically complete within 1 h at 23 °C. The amide products are isolated by an aqueous workup procedure and are purified by flash-column chromatography on silica gel. Representative examples using DIF-DMA for primary amide activation are shown in Table 2, and examples using DMF-DMA for activation are shown in Table 3. As in the scandium triflate procedure

Table 2. Transamidation Using DIF-DMA as the Activator and Zirconium Chloride as the Lewis Acid Additive[c]



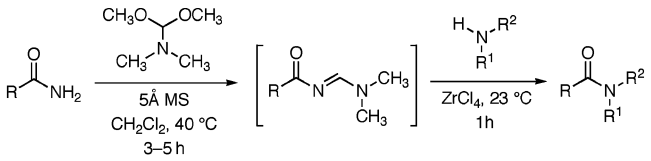
Entry	Substrate	Amine	Product	Yield
1				93%
2				97%
3				94%[a]
4				87%[b]
5				87%
6				66%
7				91%
8				94%[a]
9				92%
10				76%[a]

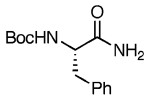
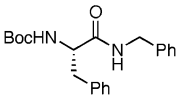
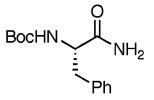
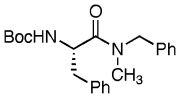
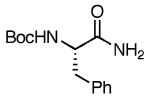
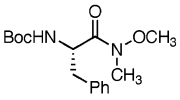
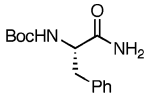
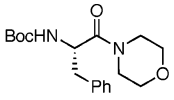
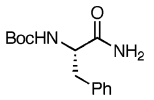
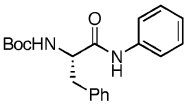
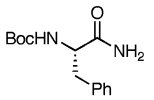
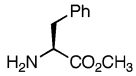
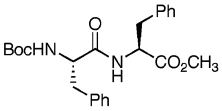
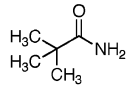
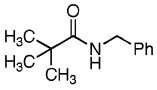
[a] Reaction employed 2.5 equiv of amine. [b] Reaction employed 3.0 equiv of amine. [c] Unless otherwise noted, reactions employed 2 equiv of amine and 0.5 equiv of zirconium chloride (as a 0.7 M solution in acetonitrile). Reported yields are for chromatographically purified products.

described above, both aliphatic and aromatic primary amides were effective substrates. Both hindered primary amide substrates (entries 7, Tables 2 and 3) and hindered amine nucleophiles (e.g., entry 9, Table 2, and entry 6, Table 3) were observed to react efficiently using zirconium chloride as the promoter. Also, with zirconium chloride as the promoter a number of transamidations of primary amides with secondary amines were observed to proceed efficiently (entries 3−6 and 8, Table 2, and entries 2−4, Table 3). Among tertiary amide products formed in this way were the synthetically useful *N*-methoxy-*N*-methyl (Weinreb) amides[10] (entry 4, Table 2, and entry 3, Table 3) and morpholino amides[11] (entry 5, Table 2, and entry 4, Table 3). This stands in contrast to results of experiments

(10) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(11) (a) Martín, R.; Romea, P.; Tey, Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414. (b) Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37.

Table 3. Transamidation Using DMF-DMA as Activator and Zirconium Chloride as Lewis Acid Additive[c]



Entry	Substrate	Amine	Product	Yield
1				94%
2				91%[b]
3				87%[b]
4				86%[a]
5				79%
6				95%
7				63%

[a] Reaction employed 2.5 equiv of amine. [b] Reaction employed 3.0 equiv of amine. [c] Unless otherwise noted, reactions employed 2 equiv of amine and 0.5 equiv of zirconium chloride (as a 0.7 M solution in acetonitrile). Reported yields are for chromatographically purified products.

with scandium triflate as the catalyst, where pyrrolidine was the only secondary amine that could be used successfully as the nucleophile (entries 2 and 3, Table 1). In this regard the two procedures are complementary, for zirconium chloride promoted transamidations using pyrrolidine as the nucleophile were less efficient than those using other secondary amines as nucleophiles (cf. entries 3−6, Table 2). A number of dipeptide derivatives were formed in high yields by zirconium chloride promoted transamidation, without detectable epimerization. These transamidations revealed that the acid-labile *tert*-butoxycarbonyl amide and *tert*-butyl ester groups were not affected under the reaction conditions (enties 8 and 9, Table 2, and entry 6, Table 3). In one case (mandelamide, entry 10, Table 2), we observed a successful transamidation in the presence of a free hydroxyl group, using DIF-DMA as the activator.[12] For most primary carboxamide substrates, zirconium chloride promoted transamidations were equivalent using either DMF-DMA or DIF-DMA for activation, although more hindered substrates such as pivalamide reacted more efficiently using DIF-DMA (cf., entries 7, Tables 2 and 3).

Conclusions

In summary, we have described two mild and efficient protocols for the transamidation of primary carboxamides. Both involve primary amide activation with *N*,*N*-dialkylformamide dimethyl acetals, forming *N*′-acyl-*N*,*N*-dialkylformamidine intermediates.[7] The latter intermediates can be subjected to transamidation directly, without purification, using zirconium chloride as a promoter (0.5 equiv) or, after purification by flash-column chromatography, using scandium triflate (0.10 equiv) as a catalyst. The procedure using scandium triflate offers the advantage of lower catalyst (promoter) loadings, whereas the procedure using zirconium chloride is more generally effective and is operationally simpler, effectively a one-flask transamidation protocol.

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Supporting Information Available: Detailed experimental procedures for all reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Although *N*′-mandeloyl-*N*,*N*-dimethylformamidine was formed cleanly using DMF-DMA as the activator and mandelamide as the substrate, attempts to achieve a subsequent transamidation with this intermediate were not successful, we speculate because of reaction (cyclization) with the free hydroxyl group.