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A Practical Preparation of Highly Versatile *N*-Acylpyrroles from 2,4,4-Trimethoxybutan-1-amine

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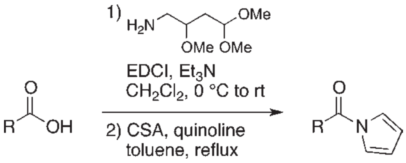
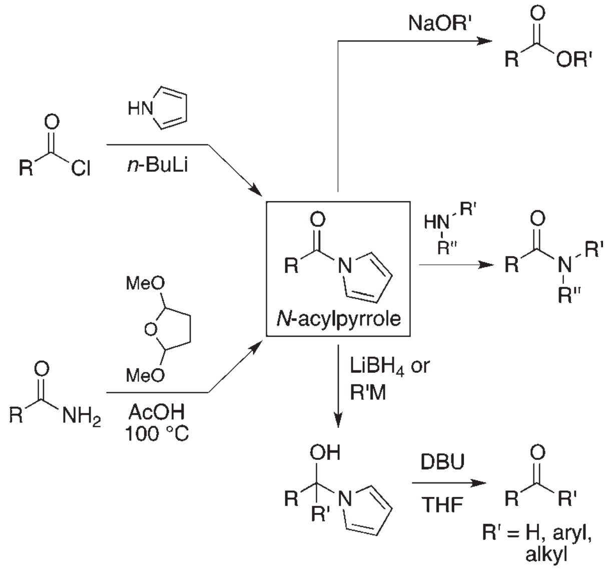
ABSTRACT



A novel method for the preparation of *N*-acylpyrrole is described. The method involves condensation of carboxylic acids with 2,4,4-trimethoxybutan-1-amine, followed by acid-mediated cyclization to form the pyrrole ring. The preparative procedure is highly tolerant of a variety of functional groups.

The unique reactivities and usefulness of *N*-acylpyrroles have been widely explored (Scheme 1). *N*-Acylpyrroles are activated acid derivatives that can react with a variety of nucleophiles, including alcohols or amines to generate the corresponding esters or amides, respectively.[1] Reactions of *N*-acylpyrroles with lithium borohydride or organometallic reagents give tetrahedral pyrrolyl carbinols with sufficient stability for isolation,[2] which could in turn be converted to aldehydes and ketones.[3] In addition, *N*-acylpyrroles have ketone-like reactivities because of the limited donation of the lone pair electrons on the nitrogen atom to the carbonyl group. This property of *N*-acylpyrroles plays an important role in organic synthesis[4] as well as in the field of asymmetric synthesis.[5]

Scheme 1. Versatility of *N*-Acylpyrrole



Typical methods for the preparation of the *N*-acylpyrroles include direct acylation of a pyrrole and condensation

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(1) (a) Lee, S.; Brook, M.; Chan, T. *Tetrahedron Lett.* **1983**, *24*, 1569. (b) Hodous, B.; Fu, G. *J. Am. Chem. Soc.* **2002**, *124*, 10006.

(2) Evans, D.; Borg, G.; Scheidt, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188.

(3) Dixon, D. J.; Scott, M. S.; Luckhurst, C. A. *Synlett* **2003**, 2317.

(4) Phippen, C. B. W.; Goldys, A. M.; Mcerlean, C. S. P. *Eur. J. Org. Chem.* **2011**, 6957.

(5) (a) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (c) Arai, Y.; Kasai, M.; Ueda, K.; Masaki, Y. *Synthesis* **2003**, 1511. (d) Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680. (e) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559. (f) Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419. (g) Park, S. Y.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 2815. (h) Kakei, H.; Sone, T.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 13410. (i) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475. (j) Zhao, D.; Wang, Y.; Mao, L.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 10983. (k) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862.

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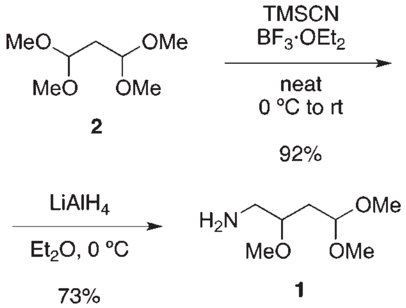
of primary amides with succinaldehyde equivalents.[1a,2,6,7] However, these methods have rather serious limitations. The former requires activation of carboxylic acids as acid chlorides and, in some cases, metalation of pyrrole. The latter requires harsh conditions such as heating in acetic acid or treatment with strong acids. These drawbacks precluded the application of *N*-acylpyrroles to the synthesis of complex molecules. Herein we report a novel method for preparing *N*-acylpyrroles under mild conditions from readily available 2,4,4-trimethoxybutan-1-amine.[8]

2,4,4-Trimethoxybutan-1-amine (**1**), a key reagent, was prepared in two steps from inexpensive 1,1,3,3-tetramethoxypropane (**2**, Scheme 2). Treatment of **2** with trimethylsilyl cyanide in the presence of boron trifluoride etherate afforded nitrile **3** in 92% yield.[9] Reduction of **3** with $LiAlH_4$ afforded, after distillation, the requisite amine **1** in 73% yield.

Scheme 2. Preparation of 2,4,4-Trimethoxybutan-1-amine (**1**)



Scheme 3. Typical Procedure for Preparation of *N*-Acylpyrrole

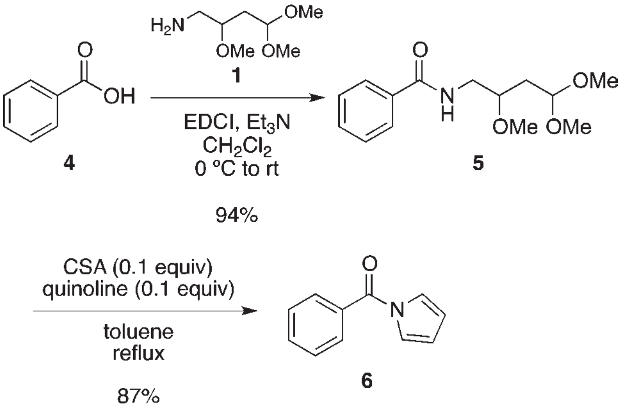
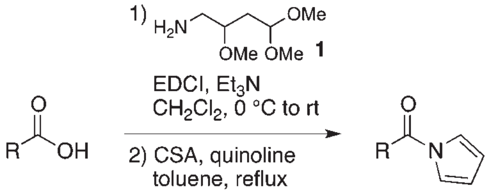
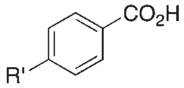
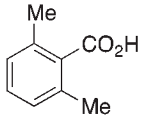
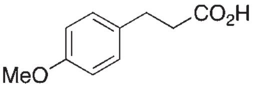
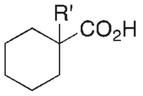
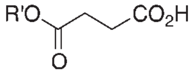
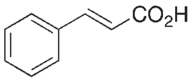
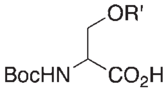
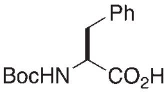


Table 1. Substrate Scope of the *N*-Acylpyrrole Synthesis[a]



entry	carboxylic acid	yield (%)[b]	
		amide	*N*-acylpyrrole
			
1	R' = Me	90	91
2	R' = OMe	78	95
3	R' = Br	72	98
4	R' = CO_2Me	76	93
5	R' = NO_2	75	93
6[c]		65[c]	95
7		89	98
			
8	R' = H	91	93
9[c]	R' = Me	46[c]	98
			
10	R' = Bn	91	97
11	R' = allyl	74	99
12		93	98
			
13	R' = MOM	72[c]	86
14	R' = TBS	86[c]	76
15		91[c]	80[d]

[a] Reaction conditions: (1) **1** (1.0 equiv), EDCI (1.5 equiv), Et_3N (1.35 equiv), CH_2Cl_2, 0 °C to rt, 1.5 h. (2) CSA (0.1 equiv), quinoline (0.1 equiv), toluene, reflux, 0.5 h. [b] Isolated yield. [c] HOBT (1.0 equiv) was added in the first step. [d] > 99% ee, determined by HPLC analysis.

Preparation of *N*-acylpyrroles involves condensation of carboxylic acids with amine **1**, followed by the

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(6) For a copper-catalyzed synthesis of di- or trisubstituted *N*-acylpyrroles, see: Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510.

(7) For the synthesis of α,*β*-unsaturated *N*-acylpyrroles via a Wittig reaction, see ref 5d. For the synthesis of α,*β*-unsaturated *N*-acylpyrroles via a Horner–Wadsworth–Emmons reaction, see ref 5f.

(8) Baran and coworkers reported the construction of a pyrrole-2-carboxylic acid moiety using a similar strategy in their synthesis of Palau'amine. Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095.

(9) Hiyama, T.; Oishi, H.; Suetsugu, Y.; Nishide, K.; Saimoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2139.

acid-mediated cyclization. A typical procedure is illustrated in Scheme 3. Condensation of carboxylic acid **4** with amine **1** proceeded smoothly by means of EDCI and Et_3N. Treatment of the resulting amide **5** with CSA (0.1 equiv) and quinoline (0.1 equiv) in refluxing toluene[10] afforded *N*-acylpyrrole **6** in good to excellent yields.

The substrate scope of the *N*-acylpyrrole synthesis is summarized in Table 1. A variety of aromatic carboxylic acids with both electron donating and withdrawing substituents on the aromatic ring were compatible with the reaction conditions, providing the corresponding products in high yield (entries 1−5). Aliphatic and α,β-unsaturated carboxylic acids could also be converted into *N*-acylpyrroles in good yields (entries 7, 8, and 10−12). Although condensation of sterically crowded carboxylic acids with **1** gave the corresponding amides in relatively low yields, formation of the pyrrole ring proceeded without difficulties (entries 6 and 9). A variety of functional groups, including Boc, MOM, and TBS groups, were compatible with the mild reaction conditions (entries 13 and 14). Furthermore, Boc-L-phenylalanine could be converted into the corresponding *N*-acylpyrrole without racemization (entry 15).

In conclusion, we have demonstrated the utility of 2,4,4-trimethoxybutan-1-amine for the preparation of *N*-acylpyrroles. A variety of functional groups could survive the mild conditions required for the transformation. Because *N*-acylpyrroles can readily be converted to carbonyl compounds such as aldehydes, ketones, esters, and amides, it is safe to say that our novel method provides access to carbonyl functionalities in the synthesis of complex molecules.

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Supporting Information Available. Experimental details and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Fukuyama, T.; Liu, G.; Linton, S.; Lin, S.; Nishino, H. *Tetrahedron Lett*. **1993**, *34*, 2577.

The authors declare no competing financial interest.