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To cite this article: Martin J. Di Grandi, Caitlin Bennett, Kristen Cagino, Arnold Muccini, Corey Suraci & Shahrokh Saba (2015): The Direct Preparation of Amides from Amine Hydrochloride Salts and Orthoesters: A Synthetic and Mechanistic Perspective, Synthetic Communications, DOI: [10.1080/00397911.2015.1096943](https://doi.org/10.1080/00397911.2015.1096943)



To link to this article: <http://dx.doi.org/10.1080/00397911.2015.1096943>

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The Direct Preparation of Amides from Amine Hydrochloride Salts and Orthoesters: A Synthetic and Mechanistic Perspective

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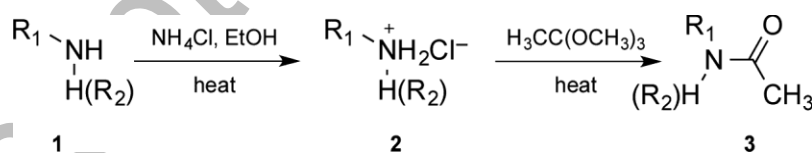
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Abstract

The conversion of a wide range of primary, secondary aliphatic and a few arylamine hydrochloride salts to their corresponding acetamides with trimethyl orthoacetate (TMOA) is described. Mechanistic studies using NMR and GC-MS techniques indicate these reactions proceed via an *O*-methylimidate intermediate that undergoes *in situ* demethylation by chloride affording the corresponding acetamides. Synthetically, this reaction represents a practical, high-yielding protocol with a simple workup for the rapid conversion of amine hydrochloride salts to acetamides.



KEYWORDS: acylation, imidate ion, orthoesters, amine hydrochlorides, amides,
microwave heating

INTRODUCTION

Acetylation is a fundamentally important reaction in both biological systems and organic chemistry. For instance, the post-translational acetylation of histone lysine residues or those found in α -tubulin is known to alter the function of these proteins and there is still a need to understand the function of *N*-terminal protein acetamides.^[1] From an organic chemistry perspective, the preparation of amides from amines is a well-established reaction,^[2] but while there exists numerous methods for this conversion, there is interest still in methods that are simple, efficient, inexpensive, and solvent- and/or catalyst-free.^[3] In light of this, we report herein our findings in the use of trimethyl orthoacetate (TMOA) as an effective acetylating agent of aliphatic/aromatic amine hydrochloride salts under either conventional heating or microwave irradiation conditions.

This work is an extension of our earlier publication that reported a highly efficient one-pot procedure for the preparation of a wide range of cyclic amidinium salts (Scheme 1).^[4] The simplicity and efficiency of this chemistry allows for the easy preparation of various 4,5-dihydroimidazolium salts, including those that feature bulky nitrogen substituents (Scheme 1: $n = 0$, $R^2 = H$), which⁵ are *N*-heterocyclic carbene precursors.^[6] Using this same methodology, we subsequently found that certain acyclic di- and tetra-alkylated amidinium salts with non-nucleophilic counterions could also be prepared from aliphatic primary and secondary monoamines upon treatment with orthoesters in the presence of ammonium tetrafluoroborate or hexafluorophosphate.^[7]

Anticipating the effect of the nucleophilicity of the anionic counterpart of the ammonium salt on the reaction course, and as part of our continued efforts on the use of simple

ammonium salts in synthetic transformations,^[8] we explored the reaction of the hydrochloride salts of primary and secondary aliphatic amines as well as a few representative anilines with TMOA. Herein, we present a simple and efficient protocol for the reaction of a series of amine hydrochloride salts (**2**, R¹ = alkyl/aryl, R² = H or alkyl) with TMOA that affords acetamides (Scheme 2).

DISCUSSION

With the exception of the commercially available hydrochloride salts of methylamine, ethylamine and the anilines, all amine hydrochloride salts (**2c-r**) used in this work were readily prepared by heating an equimolar mixture of the amine free base with ammonium chloride in ethanol (Scheme 2).^[9] These reactions were practically complete within 2 hours affording very high yields (> 90 %) of the hydrochloride salts upon removal of ethanol under reduced pressure.

In our first attempt to prepare acetamides directly from these salts, amine hydrochlorides were treated with a slight excess of TMOA at reflux under conventional heating. These reactions generally reached completion within 1-4 hours and very high yields of nearly pure acetamides were obtained upon removal of methanol and excess TMOA by rotary evaporation (Table 1).^[10] Primary and secondary amine hydrochlorides afforded very high yields of acetamides upon reaction with TMOA, but as expected, secondary amines with relatively bulky substituents (e.g., diisopropylamine) produced only traces of product.^[11] All acetamides were characterized by their ¹H and ¹³C NMR spectra, which exhibited features typical for these compounds: chemical shift nonequivalence of the *N*-

alkyl residues for tertiary acetamides^[12] and CH-NH coupling for secondary acetamides.^[13]

Following the success of this reaction, we attempted the same conversion using microwave irradiation. Gratifyingly, treatment of the same amine hydrochloride salts with 1.5 equivalents of TMOA in methanol at 135 °C for fifteen minutes cleanly afforded the corresponding acetamides (Table 1)^[9,14], in yields comparable to the thermal reaction but with substantially reduced reaction times.^[15] The only exceptions to this were the anilines (**2s** - **u**): these microwave reactions afforded highly colored crude products that required further purification via recrystallization from water/ethanol mixtures. For this reason, the anilines afforded acetanilides in lower yield, when compared to the reactions performed under conventional thermal conditions.

In terms of a plausible mechanism, this reaction appears to be driven by loss of chloromethane (Scheme 3). The ammonium chloride first catalyzes the formation of imidate **4** after loss of methanol, which is followed by subsequent *O*-demethylation by chloride, to afford the acetamide product. The intermediacy of an imidate ion was verified by the reaction of hexamethyleniminium tetrafluoroborate (**5**) with TMOA, which produced the isolable salt **6** (Scheme 4). The ¹H and ¹³C NMR spectra of this compound showed signals expected for all nonequivalent hydrogens and carbons, respectively, and the DEPT-135 spectrum of **6** displayed positive peaks for the carbons of CH₃O- and CH₃- groups of this molecule (60.0 and 14.5 ppm, respectively) and negative signals for all six methylene carbons (52.0, 50.0, 26.6, 26.3, 26.1, and 25.7 ppm,

respectively). Additionally, nucleophilic attack of the chloride ion on intermediate **4** was also inferred by isolation of MeI as by-product of the reaction of the iodide salt of hexamethyleneimine with TMOA, which was distilled from the reaction mixture and characterized by ¹H NMR and GC-MS analyses.

The literature on the reaction of aliphatic amines with TMOA is sparse and the products obtained from the reported cases vary with the reaction conditions. Most recently, Gopalan *et al.* reported the conversion of unprotected amino acids to ethyl ester acetamides in refluxing toluene containing one equivalent of triethyl orthoacetate (TEOA).^[16] Prior to this, Taylor and Ehrhart^[17] observed formation of amidines from the reaction of 2 equivalents of cyclohexylamine or benzylamine with TEOA in either the presence or absence of acetic acid as a catalyst. Swaringen, Jr. *et al.*^[18] reported a single reaction between morpholine and TMOA affording a mixture of *N*-acetylmorpholine and *N*-methylmorpholine. However, when the same amine was treated with triethyl orthoformate and *p*-toluenesulfonic acid or acetic acid as catalyst, only trimorpholinomethane was obtained as the major product. McElvain and Tate^[19] also reported a single reaction leading to *N,N*-dibutylacetamide by heating an excess of dibutylamine with TEOA at 200-220 °C for 12 hours in a bomb. The methodology reported here represents the first systematic study of this reaction and has yielded a reproducible, expedient process for the acetylation of amines under relatively mildly acidic conditions.

CONCLUSION

We have devised a practical, high-yielding protocol with short reaction times (for the microwave assisted version) and a simple workup for acetylation of the hydrochloride salts of primary and secondary amine as well as anilines using TMOA as the acetylating reagent, and we provide some mechanistic insight for this reaction. Given the importance of amine acylation as a fundamental reaction in organic synthesis and the paucity of literature data on the reaction of acyclic and cyclic aliphatic amines with TMOA, the procedure described herein highlights the utility of orthoesters as amine acylating reagents. The reaction appears to be broadly applicable to a wide variety of amines, has the distinct advantage of requiring only mildly acidic conditions and a simple workup.

EXPERIMENTAL

General Information

All solvents and reagents were obtained from commercial suppliers. With the exception of methylamine hydrochloride, ethylamine hydrochloride, and aniline hydrochlorides, all amine hydrochlorides were prepared by treatment of the amine free bases with ammonium chloride (see general procedure for the preparation of amine hydrochloride salts **2c-2r**). Pyrrolidine, piperidine, and morpholine were distilled prior to conversion to their hydrochloride salts but all the other amines were used without further purification. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of acetamides **3a-3r** and tetrafluoroborate salt **6** were recorded on a Bruker Avance DPX 300 spectrometer in CDCl_3 with TMS as the internal standard. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra of acetamides **3s-3u** were recorded on a Bruker 400 spectrometer in CDCl_3 with TMS as the internal standard. Chemical shifts are reported in ppm (δ) and J values are in Hz.

General Procedure For The Preparation Of Acetamides 3a-U: *N*-Methylacetamide

(3a)

Methylamine hydrochloride (0.68 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 0.66 g (91%) of a clear liquid. ^1H NMR δ 6.46 (br, 1H), 2.78 (d, 3H, $J_{\text{CH-NH}} = 4.8$ Hz), 1.99 (s, 3H); ^{13}C NMR δ 171.0, 26.2, 22.8.

ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the National Science Foundation Division of Undergraduate Education through Grant DUE #9650684 for the Bruker Avance 300 MHz NMR spectrometer at Fordham University. The authors also thank James A. Ciaccio for obtaining the GC-MS data and helpful comments on the manuscript.

SUPPLEMENTAL MATERIAL

Full experimental details, IR, ^1H NMR, and HRMS data for this article can be accessed on the publisher's website.

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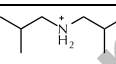
[4] This method provides a highly efficient one-pot procedure for the preparation of a wide range of cyclic amidinium tetrafluoroborate (BF_4^-) and hexafluorophosphate (PF_6^-) salts (Scheme 1) by treating primary or secondary diamines with an equimolar quantity each of an orthoester and NH_4BF_4 or NH_4PF_6 ; see: Saba, S.; Brescia A.; Kaloustian, M. *Tetrahedron Lett.* **1991**, *32*, 5031-5034.

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- [10] Diisopropylamine is known to perform poorly in acylation reactions; see reference 3a.
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- [13] The hydrochloride salts are only sparingly soluble in neat trimethyl orthoacetate, and in a few instances, some insoluble salt remained after microwave heating for 15 minutes, which resulted in incomplete conversion. The addition of methanol afforded homogeneous mixtures, thus allowing the reaction to go to completion.
- [14] Not surprisingly, this reaction is quite sensitive to moisture. Of all the amine salts tested, pyrrolidine hydrochloride (**2o**) was the most hygroscopic, turning the crystalline solid into an oil. If this oil was used under the described conditions, the reaction failed to go to completion, even under prolonged heating. Presumably, in the presence of a weak acid, adventitious water hydrolyzes TMOA, essentially terminating the reaction.

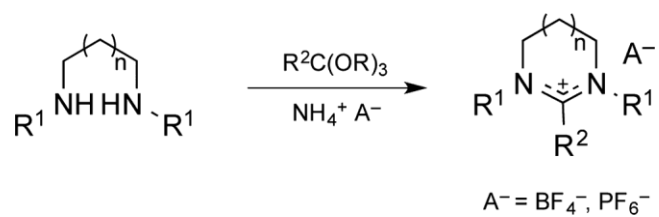
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Table 1. Preparation of secondary and tertiary acetamides

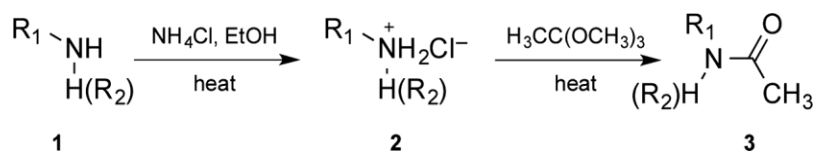
Entry	Amine.HCl Salt	Product		Thermal Reaction		Microwave Reaction ^b	
				Time (h)	Yield (%) ^a	Yield (%) ^a	
1	CH ₃ NH ₃ ⁺	2a	CH ₃ NHAc	3a	2	91	100
2	CH ₃ CH ₂ NH ₃ ⁺	2b	CH ₃ CH ₂ NHAc	3b	2	85	95
3	(CH ₃) ₂ CHNH ₃ ⁺	2c	(CH ₃) ₂ CHNHAc	3c	2	93	82
4	(CH ₃) ₃ CNH ₃ ⁺	2d	(CH ₃) ₃ CNHAc	3d	2.5	90	94
5	PhCH ₂ NH ₃ ⁺	2e	PhCH ₂ NHAc	3e	2	98	100
6		2f		3f	2	99	98
7		2g		3g	2.5	100	96
8		2h		3h	2	96	90
9		2i		3i	3	100	100
10		2j		3j	3	90	96
11	(CH ₃ CH ₂) ₂ NH ₂ ⁺	2k	(CH ₃ CH ₂) ₂ NAc	3k	4	88	77
12	(CH ₃ CH ₂ CH ₂) ₂ NH ₂ ⁺	2l	(CH ₃ CH ₂ CH ₂) ₂ NAc	3l	4	99	90
13		2m		3m	3.5	94	82
14		2n		3n	3	98	96
15		2o		3o	4	90	90
16		2p		3p	4	95	89
17		2q		3q	2	99	86
18		2r		3r	2	97	96
19	C ₆ H ₅ NH ₃ ⁺	2s	C ₆ H ₅ NHAc	3s	1	83	50
20	4-CH ₃ C ₆ H ₅ NH ₃ ⁺	2t	4-CH ₃ C ₆ H ₅ NHAc	3t	1	84	54
21	4-CH ₃ OC ₆ H ₅ NH ₃ ⁺	2u	4-CH ₃ OC ₆ H ₅ NHAc	3u	1	78	48

^aIsolated yield; ^bAll microwave reactions were complete within 0.25 h

Scheme 1 The one-pot procedure for the preparation of cyclic amidinium salts (see reference 4).

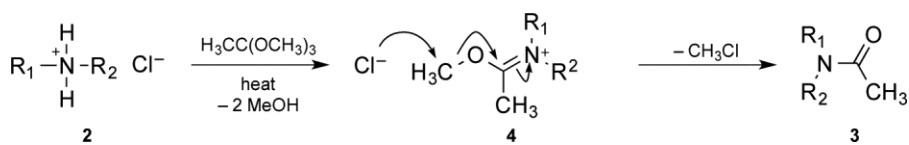


Scheme 2 The preparation of amine hydrochloride salts and their conversion to acetamides in the presence of trimethylorthoacetate.



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Scheme 3 A proposed mechanism for the conversion of amine hydrochloride salts to their acetamides in the presence of trimethylorthoacetate.



Scheme 4 The preparation of isolable salt **6** from the reaction of hexamethyleneiminium tetrafluoroborate with TMOA.

