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Tetramethyl Orthosilicate (TMOS) as a Reagent for Direct Amidation of Carboxylic Acids

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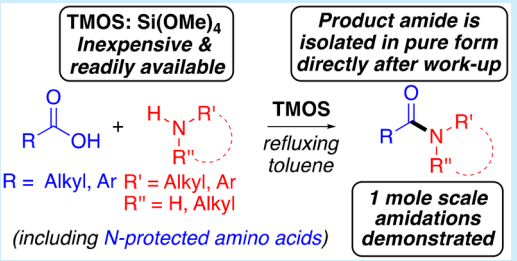
Supporting Information

ABSTRACT: Tetramethyl orthosilicate (TMOS) is shown to be an effective reagent for direct amidation of aliphatic and aromatic carboxylic acids with amines and anilines. The amide products are obtained in good to quantitative yields in pure form directly after workup without the need for any further purification. A silyl ester as the putative activated intermediate is observed by NMR methods. Amidations on a 1 mol scale are demonstrated with a favorable process mass intensity.



Methodologies that facilitate direct amidation of a carboxylic acid with an amine avoiding poor atom economy are of much current interest.[1−3] Significant progress has been made with thermal amidations,[4] boron based catalysts[5] and reagents,[6] oxophilic transition metal catalysts,[7] and other systems.[8] However, limitations remain, including multistep synthesis of catalysts, the use of nonstoichiometric acid-to-amine quantities, extended reflux with azeotropic removal of water in refluxing aromatic solvents, the need for chromatographic purification of the amide product, and/or the inability to mediate the more challenging amidation types.[9] In the mid-2000s, a series of seminal papers by Mukaiyama describe the use of imidazoylsilanes,[10] tetrakis(pyridine-2-yloxy)silane,[11] and tetrakis(1,1,1,3,3,3-hexafluoro-2-propoxy)-silane[12] as reagents for direct amidation reactions at room temperature in ethereal solvents. These silicon-based reagents perform excellently for all the major classes of acid−amine combinations, but require prior synthesis from tetrachlorosilane, and with the exception of the latter silane, they do not afford pure amide upon workup: further purification is required to remove the ancillary ligand. In addition, other silicon-based reagents[13] and silicas[14] have also been found to be useful in amide synthesis. A recent perspective[15] from industry on amidation technologies states "The ideal reagent is inexpensive, widely available, nontoxic, safe, simple to handle, easy to purge from reaction mixtures, and contributes only minimally to waste streams". This desire for convenient and inexpensive reagents, coupled with the literature precedent for silicas as reagents for amidation, prompted us to investigate the widely available and inexpensive tetraalkyl orthosilicates [$Si(OR)_4$; R = Me (TMOS, **1**), Et (TEOS, **2**)] as potential direct amidation reagents.[16,17]

We now report that TMOS **1** is an excellent reagent for effecting direct amidations, where preliminary comparisons with TEOS **2** showed the former to be more effective.[18] Thus, at 200−250 mol % TMOS **1** (for optimization of the TMOS loading, see Supporting Information (SI)) loading in refluxing toluene, direct amidation of phenylacetic acid as a representative aliphatic acid with a primary amine, cyclic secondary amines, an acyclic secondary amine, and an aniline—amidations of increasing difficulty—gave amides **3**−**7** in excellent to quantitative yield (Figure 1, top). Notable features of this amidation protocol include the use of the ideal 1:1 stoichiometry of acid and amine, the toleration of nondried toluene, and *the isolation of the pure amide product directly after a simple workup procedure*. The workup procedure acts to destroy any excess TMOS **1** or any other residual silicon-containing components, by rapid basic hydrolysis in a homogeneous THF−aqueous potassium carbonate solution to produce silica, followed by addition of solid sodium chloride to effect phase separation (see Supporting Information for full details). Any residual amidation components are also removed in the workup procedure allowing for the isolation of the amide product in pure form without the need for chromatography.

This protocol also successfully transfers to the inherently more difficult amidations of benzoic acid as a representative aromatic carboxylic acid with primary amines and cyclic secondary amines giving amides **8**−**10** (Figure 1, bottom) making this method highly competitive with other methods reported for these direct amidation classes.[4−14] To effect the still more challenging amidations of benzoic acid with acyclic secondary amines and anilines to give amides **11** and **12**, higher reaction concentrations, an excess of carboxylic acid (for **12**), and the use of 4 Å MS sieves suspended in the reaction headspace were necessary.[19−22] There is only limited literature

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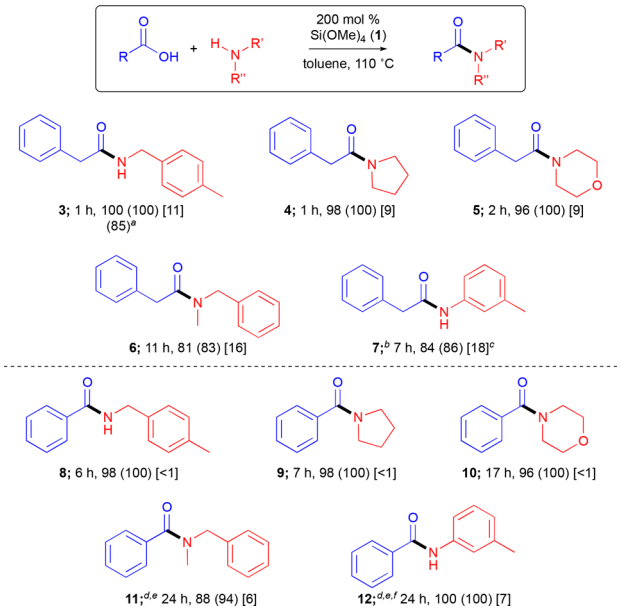
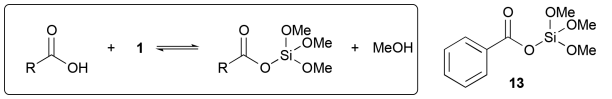


Figure 1. Direct amidations of phenylacetic acid (top) and benzoic acid (bottom) as representative aliphatic and aromatic carboxylic acids with [acid] = 0.2 M, [amine] = 0.2 M. Isolated percentage yields after workup are shown, where the value in parentheses is the percentage conversion. The value in square brackets is the percentage background conversion without added TMOS **1** under the stated conditions. All reactions were performed in triplicate; the variation in observed percentage conversions are ±1%. [a] 200 mol % TEOS **2**. [b] [acid] = 0.5 M, [aniline] = 0.5 M; 250 mol % TMOS. [c] Background conversion after 16 h. [d] 250 mol % TMOS, N_2; [acid] = 2.0 M, [amine] = 2.0 M. [e] With 4 Å MS suspended in the head space. [f] 2 equiv of BzOH (the conversion to amide **12** using 1.1 equiv of BzOH was 84%).

precedent for high yielding reactions of the former[5l,m,n] and latter[5l] amidation reaction types, and to the best of our knowledge, no quantitative yields have been reported. The quantitative yield obtained for amide **12** is therefore notable.[23] In all cases the amide products were obtained in pure form directly after workup.

Mechanistically, we consider that silyl esters[24] are the likely *de facto* acylating agents in these direct amidation reactions by formation as per the equilibrium shown in Scheme 1. In accord

Scheme 1. Silyl Esters as Postulated *de Facto* Intermediates



with this hypothesis, silyl ester **13**[25] was observed by ^{1}H, ^{13}C, and ^{29}Si NMR as the only other species as a minor component when benzoic acid was heated with TMOS in toluene for 1 h (see Supporting Information).[26,27] Furthermore, when aliquots were taken from a TMOS mediated direct amidation of benzoic acid with benzylamine (1 M in both components), the characteristic ^{1}H NMR resonances for silyl ester **13** (ca. 4%, 5 h) could also be observed.

Further exemplification of the method using branched aliphatic carboxylic acids, and *ortho*-substituted benzoic acids as amidations of increased difficulty gave amides **14**–**18** in good to quantitative yields (Figure 2). The method was further utilized to obtain Moclobemide **19** (an antidepressant),

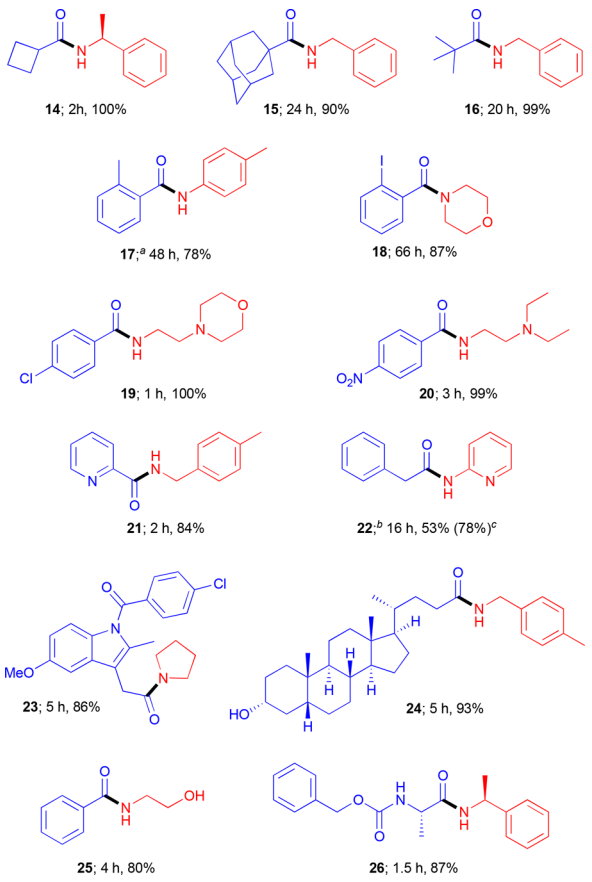


Figure 2. Direct amidations with TMOS **1** from the corresponding carboxylic acid (shown in blue postamidation) and amine/aniline (shown in red postamidation). Reaction conditions: toluene, reflux, N_2, 200 mol % TMOS **1**, [acid] = 0.2 M, [amine] = 0.2 M. [a] toluene, reflux, N_2, 250 mol % TMOS, N_2, [acid] = 4.0 M, [amine] = 2.0 M. [b] Toluene, reflux, N_2, 250 mol % TMOS, N_2, [acid] = 1.0 M, [amine] = 0.5 M. [c] Conversion.

nitrobenzenamide **20** (a viable precursor to the antiarrhythmic agent procainamide),[28] and amides **21** and **22** containing basic heterocyclic rings from their corresponding acids and amines. These examples, and the amidation of the heteroaromatic indomethacin to give amide **23**, reveals the functional group tolerance of the method. Free hydroxyl groups are tolerated either in the acid or amine component as evidenced by amidation using lithocholic acid or ethanolamine to give amides **24** and **25**. In these reactions, the hydroxyl groups presumably undergo silylation, but the resulting silyl ethers are cleaved in the workup procedure.[29] We were delighted to observe that a *N*-Cbz[30,31] protected amino acid underwent direct amidation providing amide **26** without detectable racemization.[32] In all cases, the amides were obtained pure directly after a suitable workup.

Having demonstrated that TMOS is an effective reagent for a range of direct amidations, we sought to exemplify the method on scale. Preliminary investigations on a 1 mol scale at 2 M concentration using benzoic acid and benzylamine as a representative acid–amine combination were unanticipatedly slow.[33] Here, we conjectured that *on this scale* quantities of methanol may be deleteriously retained in the reaction mixture. Accordingly, a 1 mol scale reaction of benzoic acid with pyrrolidine (Scheme 2) with fractional distillation of methanol gave a 91% conversion to product after 12 h at reflux and, after

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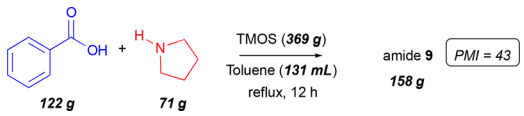
Scheme 2. 1 mol Scale Amidation To Give Amide 9



suitable workup, gave pure amide **9** in 90% isolated yield (158 g), with a process mass intensity (PMI) of 43 (see Supporting Information). A comparison of green chemistry metrics for amide-forming reactions has recently been reported: the PMI of this method compares favorably with representative conditions for those reported therein via acid chloride (PMI: 292) versus HATU (PMI: 178) versus boric acid catalysis (PMI: 89).[34]

In conclusion, we have reported the use of TMOS **1** as a readily available and inexpensive commodity for the high yielding direct amidation of representative aliphatic and aromatic carboxylic acids with primary, cyclic, and acyclic secondary amines and anilines (i.e., increasingly difficult amidations)[9] including the first quantitative direct amidation of an aromatic carboxylic acid with an aniline. The one-pot protocol, which does not require dried toluene nor necessitates preactivation of the carboxylic acid, is operationally simple, and the workup—annihilating any excess reagent and other silicon species by its conversion to silica gel—provides the pure amide products directly in excellent to quantitative yield without the need for chromatographic purification. A range of other biologically/medicinally relevant and/or challenging direct amidations are demonstrated. The method is amenable to scale-up with competitive process mass intensities compared to other procedures.[35]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03841.

General experimental; Optimization of TMOS loading; Experimental details and characterizing data for compounds; Copies of ^{1}H and ^{13}C spectra for all compounds; HPLC analysis for amide **26**; *In situ* observation of the *de facto* acylating agent by ^{1}H, ^{13}C, and ^{29}Si NMR; Green metrics (PDF)

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Notes

The authors declare no competing financial interest.

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(17) $(EtO)_4Si$ (TEOS, bp 168 °C) and $(MeO)_4Si$ (TMOS, bp 121 °C) are clear, colourless liquids and are commercially readily available (TEOS ≈ US$5 per mole; TMOS ≈ US$14 per mole). These compounds react slowly with water at neutral pH but more rapidly in acidic conditions and even more so in basic solution. They can be stored without special precautions and handled in air for short periods without significant hydrolysis.
(18) For a direct comparison, see Figure 1, amide 3, footnote a. It is our expectation that TEOS **2** would mediate all the transformations described herein, but less efficiently.
(19) The conversions to amides **11** and **12** in refluxing toluene, [acid] = 2.0 M, [amine] = 2.0 M, 250 mol% TMOS **1**, 24 h were 53% and 46% respectively.
(20) The attempted use of neat TMOS for this amidation provided amide **12** in 30% conversion. Conditions: 250 mol% TMOS, reflux, N_2, [BzOH] = 2.7 M, [*m*-$MeC_6H_4NH_2$] = 2.7 M, 24 h. The use of neat TMOS for other amidations reported herein also provided no advantage. We have also found that the use of neat TEOS **2** (bp 168−169 °C), neat $HSi(OEt)_3$ (bp 134−135 °C), or neat $B(OiPr)_3$ (bp 139−141 °C) at reflux for the direct amidation of benzoic acid with aniline at [1 M] for 7 h provided the desired amide product in 55−65% isolated yield.
(21) The attempted use of imidazole, DMAP, 1-methyl imidazole-*N*-oxide, or pyridine *N*-oxide as activating additives for this reaction led to lower conversions to the amide product than without. Conditions: Toluene, reflux, N_2, 10 mol% additive [BzOH] = 2.0 M, [*m*-$MeC_6H_4NH_2$] = 2.0 M, 250 mol% TMOS, 24 h. Conversion to amide **12**: imidazole (24%); DMAP (20%); 1-methyl imidazole-*N*-oxide (18%); pyridine *N*-oxide (28%). For the beneficial use of *N*,*N*-dimethylaminopyridine *N*-oxide in conjunction with a boronic acid catalyst for direct amidations, see ref 5l. For the beneficial use of 1-methylimidazole-*N*-oxide (NMI-O) in acylation and sulfonylation and silylation reactions of alcohols, see Murray, J. I.; Spivey, A. C. *Adv. Synth. Catal.* **2015**, *357*, 3825−3830 and references cited therein.
(22) We have not attempted the use of xylenes or mesitylene (see e.g., ref 5a) for these reactions, since their higher boiling points make them difficult to remove subsequently.
(23) In this amidation, where 2 equiv of carboxylic acid were employed, 27% of methyl benzoate (based on % of amide product) was observed in the crude reaction mixture [^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.05−8.03 (m, 2H) and 3.91 (s, 3H) ppm]. After workup, no methyl ester was observed, and we invoke basic hydrolysis of the ester in the workup procedure to rationalize this. Simulated hydrolysis of authentic methyl benzoate under the workup conditions confirmed this. Methyl benzoate has previously shown *not* to react with excess aniline neat at 140 °C Ali, Md. A.; Siddiki, S. M. A. H.; Onodera, W.; Kon, K.; Shimizu, K.-i. *ChemCatChem* **2015**, *7*, 3555−3561. Thus, it is to be expected that any methyl benzoate is kinetically stable under these conditions and will not undergo conversion to the amide.
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(30) An attempted amidation of *N*-Boc-proline with benzylamine under the standard conditions led to partial *tert*-butyl transfer to benzylamine. Column chromatography provided the pure Boc-L-proline-benzamide product in 79% yield; mp 124−125 °C (lit.[6b] 124−125 °C); $[\alpha]_D^{25}$ −80.0 (*c* 1.0, CH_2Cl_2); lit.[6b] $[\alpha]_D^{25}$ −77.0 (*c* 1.0, CH_2Cl_2).
(31) Attempted amidation of *N*-Fmoc-alanine with (*S*)-(−)-α-methylbenzylamine under the standard conditions led to the observation of 9-methylene-9*H*-fluorene as the major component in the ^{1}H NMR spectrum after workup.
(32) The diastereomeric purity of amide **26** was ascertained by comparison of the product of the same amidation reaction using D-*N*-Cbz-Ala (see SI for HPLC trace).
(33) A 1 mol reaction between benzoic acid and benzylamine (reaction conditions: toluene, reflux, 250 mol % TMOS, N_2; [BzOH] = 2.0 M, [$BnNH_2$] = 2.0 M) gave only a 51% conversion to the desired amide after 13 h. The reaction vessel was subsequently fitted with a fractional distillation column and takeoff head. After 3 h of subsequent reflux, and collection of methanol, the reaction had proceeded to 100% conversion. After workup the product was obtained pure in 99.3% yield (210 g, PMI: 20), mp 104.2−104.9 °C; lit. mp 104−105 °C: Xu, X.; Li, P.; Huang, Y.; Tong, C.; Yan, Y. Y.; Xie, Y. *Tetrahedron Lett.* **2017**, *58*, 1742−1746.
(34) Fennie, M. W.; Roth, J. M. *J. Chem. Educ.* **2016**, *93*, 1788−1793 and references cited therein. The PMI for this 1 mol scale TMOS mediated direct amidation remains unoptimized.
(35) ^{1}H NMR and ^{13}C NMR data are available via a data repository: Santhakumar, G.; Braddock, D. C.; Pugh, D. Imperial College HPC Data Repository, **2017**; DOI: 10.14469/hpc/3437.

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