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Methyltrimethoxysilane (MTM) as a Reagent for Direct Amidation of Carboxylic Acids

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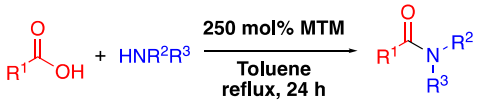

ABSTRACT: Methyltrimethoxysilane, (MTM, $CH_3Si(OMe)_3$) has been demonstrated as an effective, inexpensive and safe reagent for the direct amidation of carboxylic acids with amines. Two simple work-up procedures have been developed that provide the pure amide product without the need for further purification. The first employs an aqueous base mediated annihilation of MTM. A second involves simple product crystallisation from the reaction mixture providing a low process mass intensity direct amidation protocol.

The direct amidation of carboxylic acids with amines is a topic of much ongoing interest,[1] due to the importance of the amide bond in medicinal chemistry,[2] and in the pharmaceutical industry.[3] State-of-the-art protocols include thermal amidations,[4] boron-based catalysts[5] and reagents[6], oxophilic transition metal catalysts,[7] silicon-based reagents,[8] and others.[9] However, the search for a sustainable direct amidation reagent that is non-toxic, inexpensive and widely available, delivers amide products in high yield with all acid-amine combinations, and proceeds with an overall low process mass intensity (PMI) that avoids chromatography continues.[10] Towards that end, we have recently reported the use of tetramethylorthosilicate [TMOS, $Si(OMe)_4$] (**1**) as a reagent for direct amidation.[11] TMOS is inexpensive and widely available, successfully mediates direct amidation of aromatic and aliphatic carboxylic acids with primary amines, secondary amines and anilines in an ideal 1:1 stoichiometry, and is annihilated to silica in a simple aqueous work-up procedure that delivers the amide product in pure form without the need for chromatographic purification. However, since hydrolysis of TMOS to silica in the lung induces silicosis, TMOS is considered fatal if inhaled (GHS H330), thereby reducing its attractiveness. Accordingly, we envisioned employing an alternative silicon-based reagent that retains the inherent reactivity of TMOS, but which cannot undergo hydrolysis to silica, and is still amenable to removal in a work-up procedure. Herein, we present methyltrimethoxysilane [MTM, $MeSi(OMe)_3$] (**2**) as a safer, (and in fact, cheaper) alternative to TMOS for the sustainable direct amidation of carboxylic acids with amines (Figure 1).

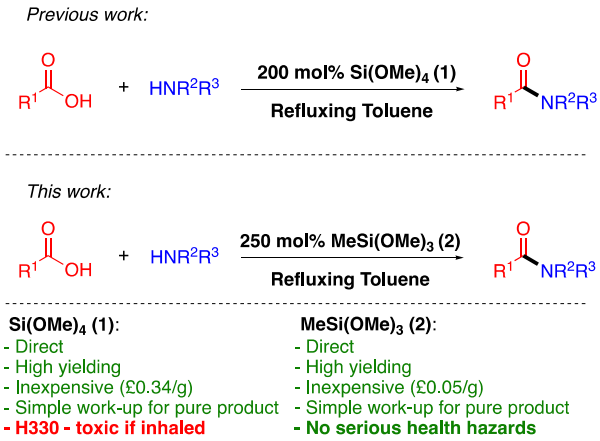

Figure 1: Previous work developed by Braddock *et al.* utilizing $Si(OMe)_4$ (**1**) as a reagent for direct amidation. This work utilizes $MeSi(OMe)_3$ (**2**).

Phenyl acetic acid and benzoic acid were chosen as representative acids to be amidated using MTM (**2**) with a representative primary amine, a secondary cyclic amine, a secondary acyclic amine and an aniline to enable a direct comparison with the use of TMOS (**1**).[11] While we were hopeful that this single 'methoxy-to-methyl' switch would not be too deleterious to reactivity, we anticipated that the work-up procedure would require significant modification to deal with the complex mixture of linear and cyclic polysiloxanes known to result on hydrolysis of MTM (**2**).[12] In the event, the use of 250 mol% MTM (for optimisation of MTM loading see the Supporting Information) in refluxing toluene provided the pure amides products **3-10** directly after a suitably modified work-up (for development of work-up procedure see the Supporting Information). Specifically, evaporation of the reaction mixture post-reaction, removes both the solvent siloxane $(MeO)_2MeSi\text{-}O\text{-}SiMe(OMe)_2$ and methanol as the expected stoichiometric by-products of the

amidation process.[13] Non-volatile oligomeric polysiloxanes were found to be completely removed after subsequent stirring of the residue in a homogeneous THF-aqueous NaOH solution for 1 hour, where any unwanted methyl ester side product also undergoes hydrolysis. Any unreacted carboxylic acid is also removed in this step, and any unreacted amine is removed in a subsequent aqueous acid wash. This work-up procedure thereby provides the amide products in pure form without the need for any further purification regardless of the extent of amidation reaction conversion.

Inspection of the isolated yields for amides **3-10** show that MTM is as effective as TMOS (**1**) as a reagent for amidation of the representative aliphatic carboxylic acid with all main amine classes. The use of benzoic acid as a representative, less reactive, aromatic carboxylic acid was high yielding with a primary amine, but less successful with secondary amines, and in contrast to the case of TMOS,[11] the attempted use of 4Å molecular sieves for these amidations either in the reaction mixture or suspended in the headspace proved to be detrimental. Pleasingly, the use of both aliphatic and aromatic carboxylic acids with aniline provided the amide products in good yields.[14]

Further exemplification of the MTM direct amidation method gave amides **11-26** (Figure 3A). These include examples of amide formation using branched carboxylic acids and amines, the use of heteroaromatic and ferrocenyl containing entities, halogenated substrates and carboxylic acids with unsaturation. Notably, both *N*-Cbz and *N*-Boc protected amino acids underwent successful amidation,[15] to give amides **22** and **23** respectively without racemisation. It is important to emphasize that all these amidations were conducted on gram scale, where the devised work-up procedure gave the pure amide product without the requirement for chromatography. However, attempts to (doubly) amidate malonic acid, or an α-hydroxy acid,[16] to form a Weinreb amide[17] or to use a low boiling amine[18] under these conditions gave the amides **27-30** (Figure 3B) in only low yield, albeit pure directly after work-up, and these experiments show the current limits of the method.

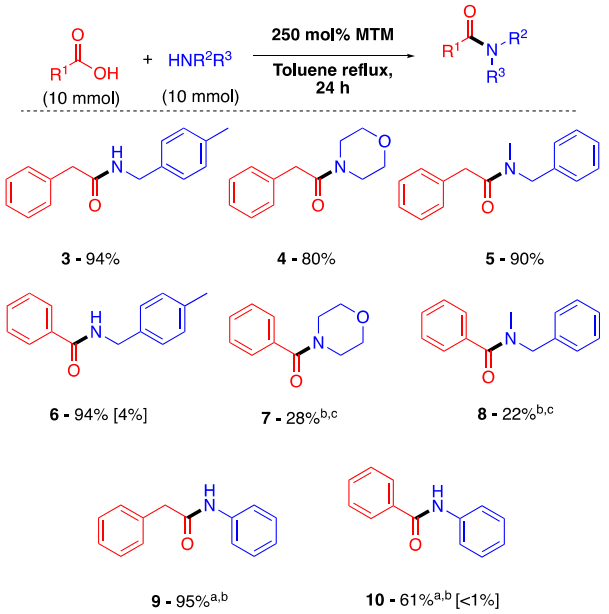

Figure 2: $MeSi(OMe)_3$ (**2**) mediated direct amidation of representative carboxylic acids and amines with [acid] = 1 M and [amine] = 1 M. [a] 2 equivalents of acid; [b] [amine] = 2 M. The isolated yield from a background reaction (*i.e.* without MTM) is given in square brackets; [c] with fractional distillation of MeOH.

As part of these investigations, we discovered that several secondary amide products crystallized from their reaction mixtures on cooling where residual MTM and its by-products remained in solution. This allowed isolation of the pure amide product directly by filtration (and a hexane wash) without the need for any further work-up , thereby resulting in low PMI values as exemplified for amides **31-32** (Figure 4).[19] To the best of our knowledge, this is the first demonstration of insolubility of secondary amides in toluene being utilized for product isolation in an amidation protocol, and we anticipate that it would be widely applicable to other secondary amide products.

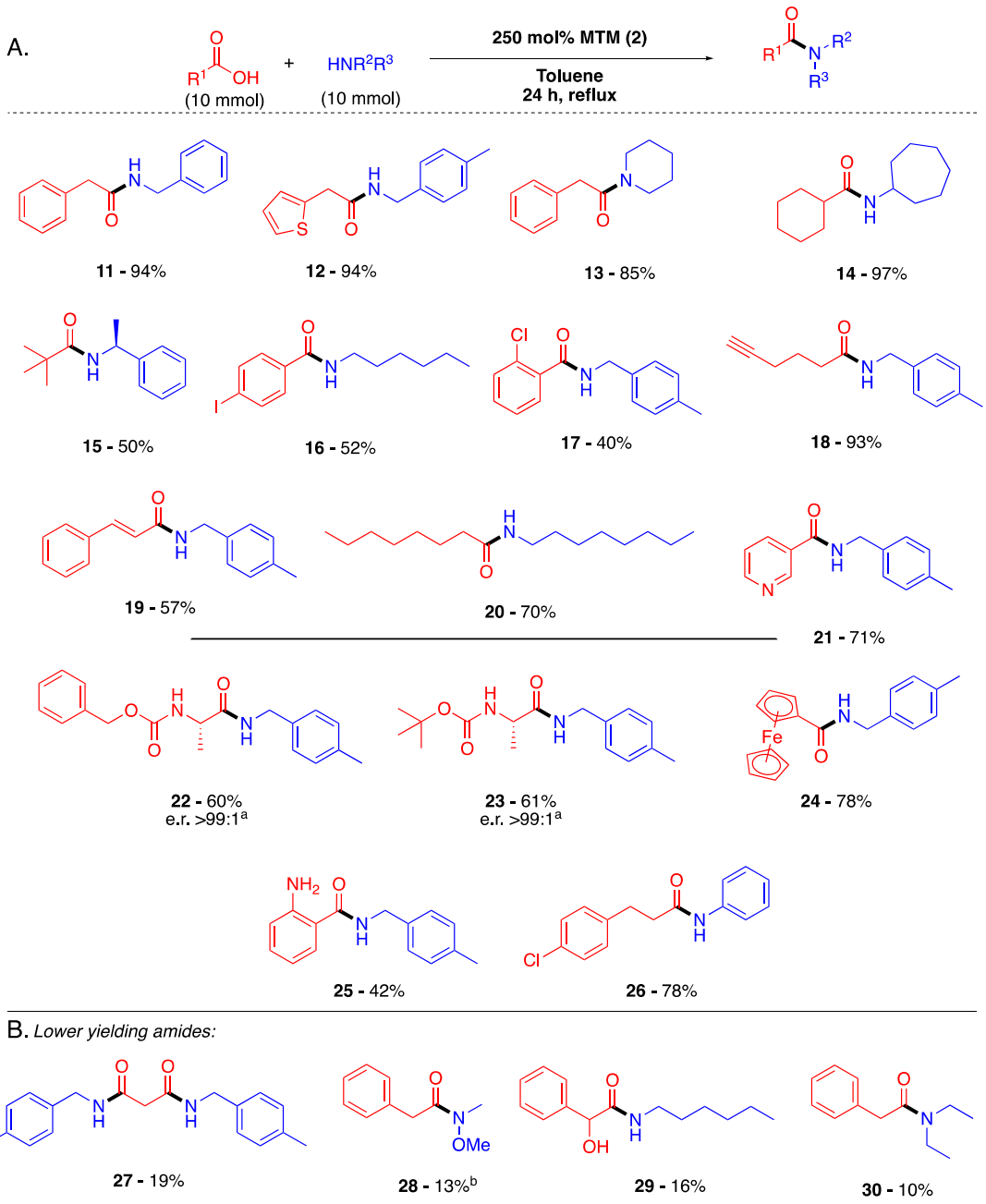

Figure 3A – Expanded scope of $MeSi(OMe)_3$ (**2**) mediated amidation of carboxylic acids and amines with [acid] = 1 M and [amine] = 1 M. **Figure 3B** – Amides formed in lower yields. [a] E.r was determined by HPLC analysis on a chiral stationary phase by reference to an authentic racemic sample. [b] 1 equiv. of NEt_3 was added to liberate amine from HCl salt.

Mechanistically, it has been proposed that amidations promoted by stoichiometric silicon reagents form silyl esters as activated intermediates.[8] We therefore propose that these amidations take place by reversible reaction of the carboxylic acid with MTM to produce a silyl ester of the type **A** with loss of methanol, followed by subsequent irreversible attack by amine to form the amide product. The liberated silanol **B** evidently must undergo favourable condensation with a second equivalent of MTM to form siloxane **C** and a second equivalent of methanol. The observation of small quantities of methyl esters (which may themselves undergo amidation) in crude reaction mixtures implicates some competitive direct attack of silyl ester **A** by methanol. In support of this mechanistic proposal, reaction of phenylacetic acid with MTM (**2**) showed the formation of an intermediate with a ^1H NMR shift at 0.42 ppm which is consistent with assignment to the $Si\text{-}CH_3$ of a silyl ester. The silyl ester was found to be completely consumed on addition of amine with concomitant amide formation.[20]

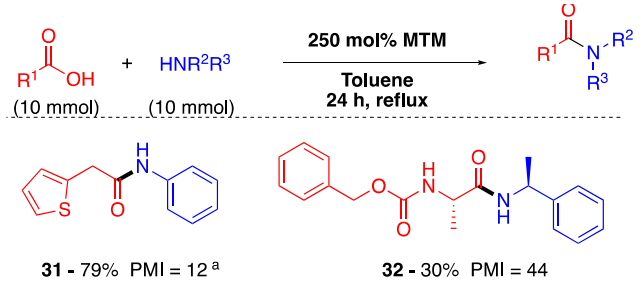

Figure 4 – Low PMI $MeSi(OMe)_3$ (**2**) mediated direct amidation of carboxylic acids and amines with [acid] = 1 M and [amine] = 1 M. [a] 45 mmol scale with fractional distillation of MeOH.

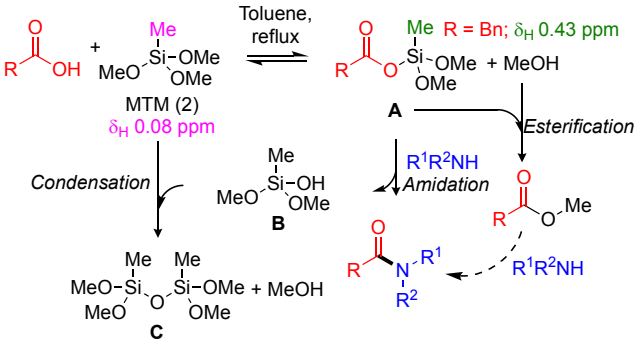

Figure 5 – Postulated mechanism for MTM direct amidations.

In conclusion, we have reported the use of MTM (**2**) as an effective, inexpensive reagent for the direct amidation of carboxylic acids with amines, providing a safe alternative to the previously published protocol using TMOS (**1**). The amide products can be isolated in pure form either via a work-up procedure which removes residual MTM and any linear and cyclic polysiloxanes reaction by-products, or (in the case of secondary amides) by simple crystallization from the reaction mixture. We expect that the latter finding will be generally applicable to provide secondary amides by this method with low process mass intensities.[21]

ASSOCIATED CONTENT

Supporting Information available: general experimental; optimization of MTM loading; optimization of work-up procedure; experimental details and characterizing data for compounds; copies of ^{1}H and ^{13}C spectra for all compounds; chiral HPLC analysis of amides **22** and **23**.

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19 Amide **3** (96%, PMI = 11), **11** (96%, PMI = 11) and **26** (78%, PMI = 14) were also isolated in pure form after crystallization.

20 Phenylacetic acid (2.45 g, 18 mmol) in refluxing toluene was stirred with MTM (5.16 mL, 36 mmol). Aliquots of the reaction mixture were analysed by ^{1}H NMR spectrocopy using durene as an internal standard. *N*-Benzylmethylamine was added after 3 h.

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