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Facile preparation of protected benzylic and heteroarylmethyl amines via room temperature Curtius rearrangement

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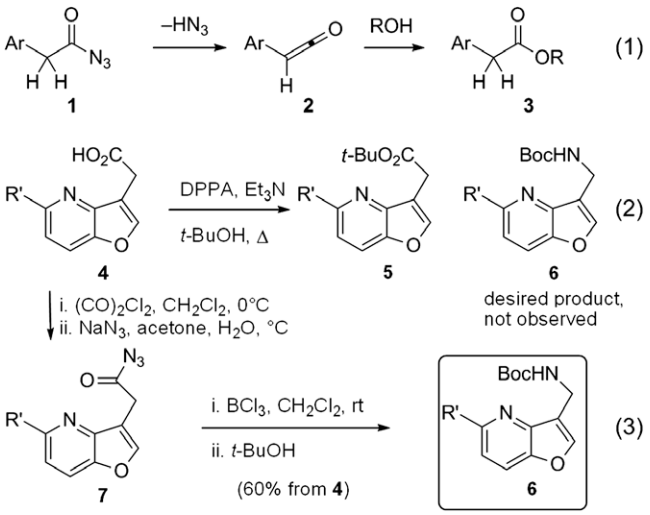
ABSTRACT

A step-wise, room temperature procedure for acyl azide formation and the subsequent Curtius rearrangement of phenyl and heteroaryl acetic acids is described. We have developed a protocol for room temperature Curtius rearrangement in MeOH or $CHCl_3$ that provides an improvement over standard conditions, avoiding the use of additives or heat. This room temperature optimization of the Curtius rearrangement prevents the formation of side products often observed with benzylic acids, allowing access to a variety of benzylic and heteroarylmethyl amines.

The Curtius rearrangement is a powerful and widely used transformation in the field of organic synthesis. The rearrangement converts an acyl azide, which can be derived from the corresponding carboxylic acid, to an isocyanate, excising a single carbon atom.[1] The isocyanate is commonly trapped by an alcohol nucleophile to generate a carbamate-protected amine. The most commonly used reagent for this transformation is diphenylphosphorylazide (DPPA), which allows the direct transformation of carboxylic acids into carbamates.[2] The use of this reagent is potentially complicated by the high temperatures required to achieve conversion to the desired carbamate, which could compromise the stability of sensitive functionalities. Furthermore, substrates that contain acidic protons adjacent to the carboxylic acid undergoing rearrangement, such as benzylic or malonic acid, are problematic for the Curtius rearrangement using DPPA, often leading to ester byproducts.[3] This could potentially occur through elimination of hydrazoic acid, formation of the ketene, and subsequent trapping with the alcohol nucleophile (Scheme 1, Eq. 1).[4] We observed this side reaction when attempting to convert acid **4** to carbamate **6** by heating **4** with DPPA and triethylamine in *t*-BuOH (Scheme 1, Eq. 2).[5] To avoid the side reaction, we found that sequential formation of the acyl azide **7** and treatment with BCl_3 at rt in CH_2Cl_2 followed by addition of *t*-BuOH led to the desired product in moderate yield (Scheme 1, Eq. 3).

The widespread abundance of benzylic amines in biologically active molecules as well as the use of benzylic amines bearing stereogenic centers as ligands in asymmetric synthesis prompted us to further explore the optimization of this procedure.[6] A general method for the formation of benzylic amines from readily available carboxylic acids would prove particularly useful, especially when considering the powerful asymmetric hydrogenation methods that have been developed for accessing α-chiral benzylic acids.[7] Herein we describe a step-wise procedure for the conversion of benzylic and heteroarylmethyl acids to carbamate-protected amines via a room temperature Curtius rearrangement.

Our first task was to screen a variety of Lewis acids and solvents with the aim of determining the optimal conditions for Curtius rearrangement of benzylic acyl azides. For this initial study, the acyl azide **9**, derived from 4-methoxybenzoic acid, was employed



Scheme 1. Formation of undesired ester byproducts.

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as our standard substrate, with MeOH as the nucleophile to trap the isocyanate.[8] A wide variety of Lewis acids and solvents were tested, with no improvement over the initial result. We made a key observation during these studies that in some instances, acyl azide **9** was not undergoing rearrangement to the isocyanate until after the addition of methanol. This observation led us to the discovery that in the presence of MeOH, **9** was cleanly converted to the desired methyl carbamate **10a** after 18 h at room temperature, in the absence of any additive (Fig. 1).[9]

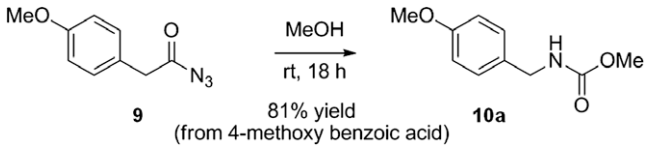
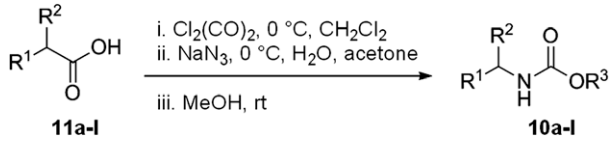
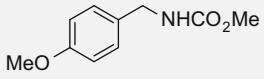
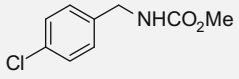
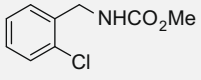
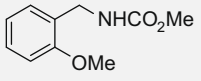
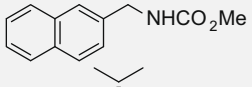
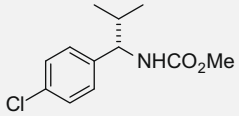
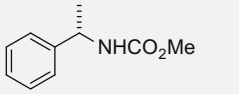
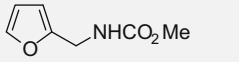
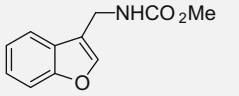
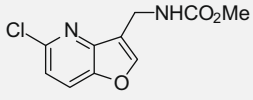
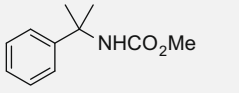
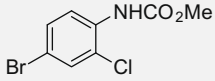


Figure 1. Room temperature Curtius rearrangement in MeOH.

Table 1
Acyl azide formation and rt Curtius rearrangement



Entry	Time	Product	Yield (%)[a]
1	18 h		**10a** 81
2	24 h		**10b** 80
3	48 h		**10c** 78
4	48 h		**10d** 87
5	24 h		**10e** 85
6	18 h		**10f** 70 (>99% ee)
7	18 h		**10g** 85 (>99% ee)
8	24 h		**10h** 61
9	24 h		**10i** 78
10	48 h		**10j** 75
11	12 d		**10k** 86
12	24 h		**10l** 92

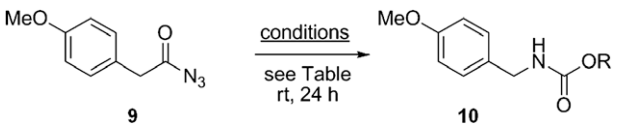
[a] Isolated yield starting from corresponding carboxylic acid.

There are few reports of low temperature Curtius rearrangements; one notable exception is the work by Lebel and co-workers where they report a useful one-pot Curtius rearrangement using $TMSN_3$, Boc_2O, and $Zn(OTf)_2$ at 40 °C.[10] The authors reveal that a benzylic acid substrate was problematic, leading to a mixture of desired product and the anticipated ester byproduct, thus highlighting the utility of our discovery. This simple solution to the problematic Curtius rearrangement of benzylic and heteroarylmethyl acyl azides is complementary to existing methods and provides an alternative procedure for more sensitive compounds that are unstable to heat or Lewis Acids. For example, the acyl azide derived from 2-(benzofuran-3-yl)acetic acid forms extensive side products in the presence of Lewis acids at room temperature or when heated with DPPA, but converts cleanly to carbamate **10i** at room temperature in methanol (Table 1, entry 9).

To determine the generality of the step-wise acyl azide formation and room temperature Curtius rearrangement in methanol, the scope of the transformation was investigated (Table 1). A wide variety of benzylic and heterocyclic acids convert to the corresponding methyl carbamates in good yield (Table 1). Chiral, nonracemic acids can also be converted to the corresponding protected amines without racemization of the adjacent stereogenic center (Table 1, entries 6 and 7). The reaction can be run under an air atmosphere without strict moisture exclusion, and purification of the resulting products is simplified by the absence of additives. In many applications, simply concentrating the reaction mixture provides product of sufficient purity for subsequent chemical transformations. Aromatic acids also undergo rearrangement cleanly in high yield (Table 1, entry 12), however aliphatic acids provide the corresponding carbamate in poor yields due to competitive hydrolysis of the acyl chloride during acyl azide formation. Substrates bearing a quaternary carbon adjacent to the acyl azide undergo the rearrangement at a slower rate, achieving 86% yield after 12 d. (Table 1, entry 11). This limitation is not especially troubling, since substrates bearing quaternary carbons will not be susceptible to ester byproduct formation using established procedures.[11] It should also be noted that increasing the reaction temperature (40–60 °C) can shorten the reaction time considerably for substrates listed in Table 1, but often leads to increased formation of undesired byproducts.

The procedure described above provides a convenient and mild method for accessing benzylic and heteroarylmethyl amines without forming ester byproducts, however, removal of methyl carba-

Table 2
Solvent screen



Entry	Solvent (condition)	Product	% Conv.[a]
1	THF, MeOH (5 equiv)	**10a**, R = Me	37
2	*p*-Dioxane, MeOH (5 equiv)	**10a**, R = Me	21
3	MeCN, MeOH (5 equiv)	**10a**, R = Me	46
4	Benzene, MeOH (5 equiv)	**10a**, R = Me	68
5	CH_2Cl_2, MeOH (5 equiv)	**10a**, R = Me	74
6	$CHCl_3$, MeOH (5 equiv)	**10a**, R = Me	87 (81)[b]
7	$CHCl_3$, MeOH (3 equiv)	**10a**, R = Me	75
8	$CHCl_3$, MeOH (1 equiv)	**10a**, R = Me	47
9	^{i}PrOH	**10m**, R = ^{i}Pr	48[b]
10	*t*-BuOH	**10n**, R = ^{t}Bu	28[b]
11	$CHCl_3$, *t*-BuOH (5 equiv)	**10n**, R = ^{t}Bu	Trace

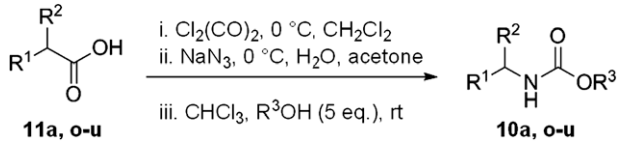
[a] Conversion to product **10** measured by HPLC–LRMS.
[b] Isolated yield.

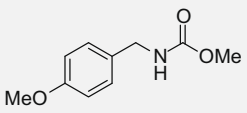
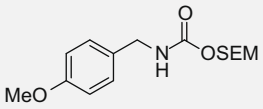
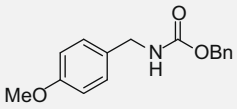
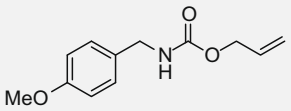
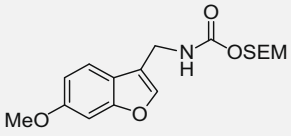
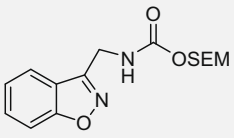
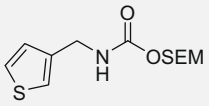
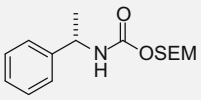
mates can often require harsh basic conditions. Thus, we sought to further expand this protocol so that alternative alcohol nucleophiles could be utilized to form more readily deprotected carbamates. A simple solution would be to perform the rearrangement in *t*-BuOH to form the Boc carbamate, however, we found that both ^{i}PrOH and *t*-BuOH provided slow conversion to products **10m** and **10n**, revealing that the steric nature of the alcohol nucleophile greatly effects the rate of product formation (Table 2, entries 9–11).

An important consideration was to determine whether the rearrangement would take place without using the desired alcohol as the solvent. This would allow the preparation of alternative carbamates that could be deprotected under more mild conditions without using excessive amounts of potentially expensive alcohol nucleophiles. A variety of solvents were screened using 5 equiv of MeOH as an additive. Chloroform was uniquely effective in providing the fastest rearrangement.[12] Comparison of entries 6–8 (Table 2) reveals that the 5 equiv of the alcohol nucleophile is the optimal condition to achieve a reasonable yield in 24 h.

Using the optimal conditions from Table 2 (entry 6) a variety of substrates and different alcohol nucleophiles were tested (Table 3).

Table 3
Formation of easily deprotected carbamates



Entry	Time	R^3OH	Product		Yield (%)[b]
1	18 h	MeOH		**10a**	77
2	18 h	SEMOH[a]		**10o**	80
3	18 h	BnOH		**10p**	82
4	18 h	Allyl-OH		**10q**	88
5	24 h	SEMOH		**10r**	90
6	72 h	SEMOH		**10s**	81
7	24 h	SEMOH		**10t**	76
8	24 h	SEMOH		**10u**	89 99% ee

[a] SEMOH = 2-(Trimethylsilyl)ethanol.
[b] Isolated yields.

Again, the transformation appears to be general for both benzylic and heteroaryl substrates with less sterically hindered nucleophiles.[13] Carbamate derivatives bearing a variety of more easily deprotected side chains were formed in good yield.

In conclusion, a simple step-wise procedure to achieve a room temperature Curtius rearrangement of benzylic and heteroarylmethyl carboxylic acids is reported. The conditions described herein provide an alternative to the already described one-pot procedures that require heating or the use of Lewis acids. It is our hope that reporting this simple result will enable others to easily prepare benzylic and heteroarylmethyl carbamates without the formation of unwanted ester byproducts or other deleterious side reactions. The mild nature of these conditions and the ease of purification will hopefully encourage their use in more complicated synthetic applications.

Experimental section

Representative synthesis of acyl azide intermediates

To a flask under nitrogen atmosphere containing 4-methoxyphenylacetic acid (**11a**, 166.2 mg, 1.0 mmol) was added CH_2Cl_2 (5 mL, 0.2 M). The resulting solution was cooled to 0 °C and oxalyl chloride (175 μL, 2.0 mmol) was added followed by DMF (39 μL, 0.5 mmol). The solution was allowed to warm to rt and maintained until gas evolution ceased (~1 h). The solution was concentrated in vacuo and the resulting residue was taken up in acetone (5 mL, 0.2 M) and transferred dropwise to a vigorously stirring aqueous solution (0.4 M) of sodium azide (130.0 mg, 2.0 mmol) at 0 °C. The resulting solution was maintained at 0 °C for 15 min, at which time it was partitioned between EtOAc (10 mL) and H_2O (5 mL). CAUTION: the aqueous layer may contain hydrazoic acid (HN_3) as a byproduct.[14] The layers were separated and the aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with deionized water (10 mL), brine (5 mL), then dried (Na_2SO_4) and concentrated in vacuo to provide acyl azide **9**, which could be stored at rt for several hours, or at –20 °C for several days without decomposition or rearrangement.[15]

Preparation of methyl carbamates (Table 2)

To a flask charged with acyl azide **9** (1.0 mmol, prepared as described above) was added 5 mL of MeOH; the solution was maintained at rt for 18 h, at which time it was concentrated in vacuo. The residue was purified by silica gel chromatography using a gradient of 2–80% EtOAc in hexanes to yield 158.0 mg (81% yield) of methyl 4-methoxybenzylcarbamate (**10a**).

Preparation of alternative carbamates (Table 3)

To a flask charged with 2-(6-methoxyubenzofuran-3-yl-)acetyl azide (0.84 mmol, prepared from 2-(6-methoxybenzofuran-3-yl)acetic acid (**11r**) analogously to azide **9**) was added $CHCl_3$ (5 mL, anhydrous, stabilized with amylenes)[13] followed by 2-(trimethylsilyl)ethanol (0.60 mL, 4.2 mmol). The resulting solution was maintained at rt for 24 h, at which time it was concentrated in vacuo. The residue was purified by silica gel chromatography using a gradient of 2% EtOAc in hexanes –100% EtOAc to yield 242 mg (90% yield) of (2-(trimethylsilyl)ethoxy)methyl (6-methoxybenzofuran-3-yl)methylcarbamate (**10r**).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.101.

References and notes

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5. This byproduct was observed by LC–MS.
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8. As a control, we tested alternate Curtius conditions (refluxing 4-methoxybenzoic acid, DPPA, Et_3N, and MeOH or *t*-BuOH), which led to numerous side products instead of rearrangement product **10a**.
9. Attempts to increase the rate of conversion to **10a** by addition of catalytic HCl, and other more acidic alchohol solvents such as hexafluoroisopropanol and trifluoroethanol led in all cases to ester byproducts in addition to product **10a**.
10. (a) Lebel, H.; Leogane, O. *Org. Lett.* **2005**, *7*, 4107–4110; (b) Yukawa, Y.; Tsuno, Y. *J. Am. Chem. Soc.* **1959**, *81*, 2007–2012; (c) Newman, M.; Gildenhorn, H. *J. Am. Chem. Soc.* **1948**, *70*, 317–319; (d) Coleman, R. A.; Newman, M. S.; Garrett, A. B. *J. Am. Chem. Soc.* **1954**, *76*, 4534–4538; (e) Fahr, E.; Neumann, L. *Angew. Chem.* **1965**, *77*, 591.
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12. Although it is possible that rearrangement could be promoted by trace amounts of HCl present in $CHCl_3$, we found that the product was formed with equal efficiency in base-washed $CHCl_3$. The hydrogen-bonding capability of $CHCl_3$ could also be responsible, see: Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662–9663.
13. Note that the majority of commercially purchased chloroform is stabilized with added ethanol, even if unspecified. Ethanol can compete with other alcohol nucleophiles to trap the isocyanate intermediate. We recommend using anhydrous chloroform stabilized with amylenes to avoid this complication.
14. See: Wiss, J.; Fleury, C.; Onken, U. *Org. Process Res. Dev.* **2006**, *10*, 349–353. and references therein.
15. Although acyl azides are a widely used intermediate in organic synthesis, the authors caution that low molecular weight acyl azides can be potentially explosive if evaporated to dryness. See: Overman, L. E.; Jessup, P. J.; Petty, C. B.; Roos, J. *Org. Synth.* **1980**, *59*, 1. On larger scale, the authors recommend partial concentration of the acyl azide intermediate, followed by introduction of MeOH.