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Three-Component Synthesis of Amine Derivatives Using Benzylic and Allylic Alcohols as *N*-Alkylating Agents in the Absence of External Catalysts and Additives

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Keywords: Multicomponent reactions / *N*-Alkylation / Alcohols / Amine derivatives / Catalyst-free reactions

The direct employment of benzylic and allylic alcohols as *N*-alkylating agents provides a useful synthetic route for amine derivatives by avoiding the preactivation of the hydroxy groups of alcohols. Herein we report a novel by-product-catalyzed three-component synthesis of amine derivatives from readily available benzylic and allylic alcohols, acyl chlorides (chloroformates or sulfonyl chlorides), and hexamethyldisilazane (HMDS). In the absence of external catalysts and additives, a range of benzylic and allylic alcohols have been transformed into the corresponding *N*-alkyl amides (carbamates or sulfonamides) in good to excellent yields. Furthermore, by-product TMSCl and its decomposition into HCl have been found to be responsible for promoting the three-component reaction of benzylic (or allylic) alcohols with acyl chlorides (chloroformates or sulfonyl chlorides) and HMDS.

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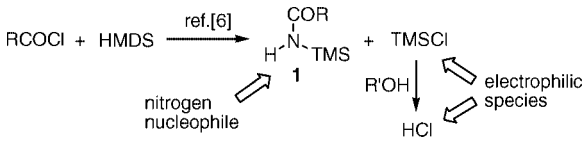
Introduction

The direct employment of readily available benzylic and allylic alcohols as *N*-alkylating agents provides a useful synthetic route for amine derivatives, which are widely applied to the synthesis of pharmaceuticals and fine chemicals,[1] by avoiding the preactivation of the hydroxy groups of alcohols.[2] In recent years a number of effective catalysts and additives were discovered for the synthesis of amine derivatives through the direct substitution of the hydroxy groups of benzylic and allylic alcohols with weak nitrogen nucleophiles such as amides, carbamates, and sulfonamides.[3,4] Nevertheless, it is more desirable for external catalysts and additives to be omitted in the synthesis of such amine derivatives. In addition, the introduction of multicomponent reaction (MCR)[5] will further facilitate the synthesis in terms of step economy.

We explored recently the reaction of RCOCl (acyl chloride or chloroformate) with HMDS, known to generate nitrogen nucleophile **1** and TMSCl (Scheme 1),[6,7] in the four-component synthesis of amine derivatives, and found that by-product TMSCl played an important role in promoting the reaction.[8] This finding prompted us to develop a by-product-catalyzed reaction[9] without external catalysts and additives by taking advantage of the fact that TMSCl, a silicon Lewis acid,[10] can be decomposed by an alcohol to generate HCl, a strong Brønsted acid (Scheme 1). We hypothesized that these electrophilic species could activate the hydroxy group of a benzylic (or allylic) alcohol to promote its substitution by a nitrogen nucleophile,[11] and envisaged an incorporation of the formation of nitrogen nucleophile **1** and its *N*-alkylation with a benzylic (or allylic) alcohol into a by-product-catalyzed three-component reaction (3CR) of benzylic (or allylic) alcohol with RCOCl and HMDS, which would not only avoid the use of external catalysts and additives in the reaction, but also save one step when compared with two sequential bimolecular reactions. The reaction of RCOCl with HMDS was expected to proceed much faster than their decomposition by an alcohol so that the proposed 3CR could afford the desired product in synthetically useful yield.



Scheme 1. Generation of nitrogen nucleophile **1**, TMSCl, and HCl.

Herein we report, for the first time, an efficient by-product-catalyzed three-component synthesis of *N*-alkyl amides (carbamates or sulfonamides) from readily available benzylic and allylic alcohols, acyl chlorides (chloroformates or sulfonyl chlorides), and hexamethyldisilazane (HMDS) in the absence of external catalysts and additives.

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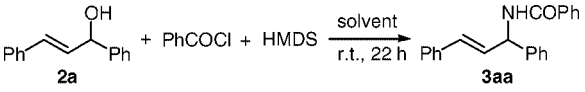
Results and Discussion

The 3CR of alcohol **2a** with PhCOCl and HMDS was selected as a model reaction to test our hypothesis (Table 1). This reaction was carried out under "pure" MCR conditions by adding HMDS and alcohol **2a** successively to a solution of PhCOCl at room temperature. The reaction was found to proceed smoothly to give product **3aa** in a range of untreated common solvents, even in ethanol (Table 1, Entry 9), and the best yield (95%) was achieved in acetonitrile (Table 1, Entry 10). The replacement of PhCOCl by PhCOBr in the 3CR resulted in the formation of product **3aa** in much lower yield (51%), and no desired product was obtained at all when PhCOF was treated with alcohol **2a** and HMDS under the same reaction conditions.

Table 1. Survey of solvents.[a]



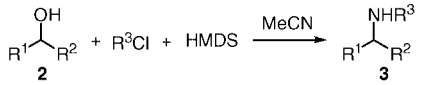
Entry	Solvent	Yield [%][b]	Entry	Solvent	Yield [%][b]
1	PhMe	52	6	Et_2O	24
2	CH_2Cl_2	89	7	THF	78
3	$CHCl_3$	70	8	dioxane	90
4	$(ClCH_2)_2$	64	9	EtOH	47
5	EtOAc	86	10	MeCN	95

[a] Reaction conditions: **2a** (0.25 mmol), PhCOCl (0.30 mmol), HMDS (0.30 mmol), solvent (0.25 mL), room temp. [b] Isolated yield.

A variety of conjugated and unconjugated acyl chlorides were found to be suitable for the three-component synthesis of *N*-alkyl amides (Table 2, Entries 1–7). Higher temperature could not only accelerate the rate of the reaction dramatically, but also improve the yield significantly. For example, the 3CR of alcohol **2a** with crotonoyl chloride and HMDS was conducted at room temperature for 54 h and gave product **3ae** in 63% yield; but when the temperature was elevated to 75 °C, the reaction time was shortened to 9 h and the yield was increased to 79% (Table 2, Entry 5). The replacement of acyl chlorides with chloroformates in the 3CR could afford the corresponding *N*-alkyl carbamates in good to excellent yields (Table 2, Entries 8–10). In contrast, the 3CR of *p*-toluenesulfonyl chloride with alcohol **2a** and HMDS in acetonitrile was unsatisfactory (75 °C, 51% yield), but a much better yield (70%) was achieved when the reaction was carried out in dioxane at 100 °C (Table 2, Entry 11). Further examination of the 3CR revealed that secondary benzylic (Table 2, Entries 13–25) and allylic (Table 2, Entries 12 and 26) alcohols were suitable substrates, and primary ones such as benzyl alcohol and allyl alcohol were not able to give the desired products under similar reaction conditions.

As expected, in the 3CR the intermediate $R^3NH(TMS)$ (R^3 = acyl, alkoxycarbonyl, or sulfonyl) was generated quickly by the reaction of HMDS with R^3Cl, and its amount decreased gradually as the reaction progressed.[12] Thus, the rest of reaction pathway for the 3CR can be treated as a bimolecular reaction of $R^3NH(TMS)$ with

Table 2. Three-component synthesis of amine derivatives.[a]

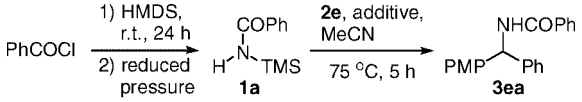


Entry	R^1	R^2	R^3	2/3	Temp/Time [°C]/[h]	Yield [%][b]
1	PhCH=CH[c]	Ph	PhCO	**2a/3aa**	25/22	95
2	PhCH=CH[c]	Ph	4-O_2N-C_6H_4CO	**2a/3ab**	25/30	81
3	PhCH=CH[c]	Ph	4-MeO-C_6H_4CO	**2a/3ac**	75/8	61
4	PhCH=CH[c]	Ph	PhCH=CHCO[c]	**2a/3ad**	75/8	70
5	PhCH=CH[c]	Ph	MeCH=CHCO[c]	**2a/3ae**	75/9	79
6	PhCH=CH[c]	Ph	MeCO	**2a/3af**	25/47	74
7	PhCH=CH[c]	Ph	*c*-C_6H_{11}CO	**2a/3ag**	25/23	72
8	PhCH=CH[c]	Ph	Cbz	**2a/3ah**	25/24	78
9	PhCH=CH[c]	Ph	Fmoc	**2a/3ai**	25/46	82
10	PhCH=CH[c]	Ph	PhOCO	**2a/3aj**	25/24	91
11[d]	PhCH=CH[c]	Ph	Ts	**2a/3ak**	100/11	70
12[d]	PhCH=CH[c]	Me	PhCO	**2b/3ba**	100/17	59
13	4-Me-C_6H_4	Ph	PhCO	**2c/3ca**	75/10	61
14	4-Me-C_6H_4	4-Me-C_6H_4	PhCO	**2d/3da**	75/33	85
15	PMP[e]	Ph	PhCO	**2e/3ea**	75/5	98
16	PMP[e]	Ph	MeCH=CHCO[c]	**2e/3ee**	75/9	65
17	PMP[e]	Ph	MeCO	**2e/3ef**	75/9	90
18	PMP[e]	Ph	PhOCO	**2e/3ej**	25/46	84
19	PMP[e]	Ph	Ts	**2e/3ek**	75/24	53
20	PMP[e]	4-Me-C_6H_4	PhCO	**2f/3fa**	75/1	96
21	PMP[e]	Me	PhCO	**2g/3ga**	75/24	67
22	4-HO-C_6H_4	Ph	PhCO	**2h/3ha**	25/14	70
23	2-MeO-C_6H_4	Ph	PhCO	**2i/3ia**	75/12	89
24	2-MeO-C_6H_4	4-Me-C_6H_4	PhCO	**2j/3ja**	75/11	89
25	2-HO-C_6H_4	Ph	PhCO	**2k/3ka**	17/24	60
26	R^1, R^2 = 		PhCO	**2l/3la**	75/10	52

[a] Reaction conditions: **2** (0.25 mmol), R^3Cl (1.2 equiv.), HMDS (1.2 equiv.), MeCN (0.25 mL). [b] Isolated yield. [c] (*E*) configuration for C=C bond. [d] The reaction was conducted in dioxane at 100 °C. [e] PMP = *p*-methoxyphenyl.

alcohol **2** in the presence of TMSCl, which was proved to promote the reaction exclusively by the following experiments. The treatment of PhCONH(TMS) (**1a**), generated from PhCOCl and HMDS, with alcohol **2e** did not afford product **3ea** at all (Table 3, Entry 1), but the addition of TMSCl to the mixture of amide **1a** and alcohol **2e** resulted in the formation of product **3ea** in 93% yield (Table 3, Entry 2), which is comparable to that obtained from the original 3CR under the same reaction conditions (98% yield, Table 2, Entry 15).

Table 3. *N*-Alkylation of amide **1a** with alcohol **2e**.



Entry	Additive	Isolated Yield [%]
1	none	0
2	TMSCl (1.2 equiv.)	93

Either in the three-component synthesis of amide **3ea** (Table 2, Entry 15) or in the TMSCl-catalyzed reaction of amide **1a** with alcohol **2e** (Table 3, Entry 2), a significant amount of alcohol **2e** was first converted into intermediate **4e** (Table 4, Entry 1),[13] which would then disappear by the

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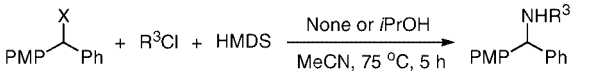
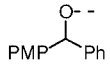
end of the reaction. The replacement of alcohol **2e** with ether **4e** in the 3CR resulted in the formation of product **3ea** in only 33% yield. Nevertheless, the addition of 2-propanol to this reaction mixture could increase the yield up to 95% (Table 4, Entry 1). When the same 3CR conditions were applied to silyl ether **5e** (a possible intermediate resulting from alcohol **2e**[14]), similar results were obtained (Table 4, Entry 2). These results suggest that the generation of TMSCl is essential for the by-product-catalyzed 3CR to take place, and the decomposition of TMSCl into HCl by an alcohol is much more effective in catalyzing the 3CR than TMSCl itself. Notably, the formation of product **3ea** could be suppressed dramatically by the addition of molecular sieves to sequester HCl in the 3CR of alcohol **2e** with PhCOCl and HMDS despite the fact that both of the intermediates, amide **1a** and ether **4e**, were generated.[15]

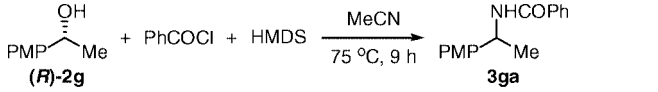
Table 4. 3CR of alcohol derivatives with R^3Cl and HMDS.[a]



Entry	Substrate	X	R^3	Product	Isolated Yield [%]	
					None	*i*PrOH
1	**4e**		PhCO	**3ea**	33	95
2	**5e**	OTMS	PhCO	**3ea**	44	96
3	**3ek**	NHTs	PhCO	**3ea**	70[b]	62[b]
4	**3ea**	NHCOPh	MeCO	**3ef**	0[b]	0[b]

[a] Reaction conditions: substrate (0.25 mmol), R^3Cl (1.2 equiv.), HMDS (1.2 equiv.), MeCN (0.25 mL), 75 °C, 5 h. [b] Determined by ^1H NMR analysis.

Although the treatment of sulfonamide **3ek** with PhCOCl and HMDS could result in the formation of benzamide **3ea** in good yield (Table 4, Entry 3), benzamide **3ea** could not be converted into acetamide **3ef** at all in the presence of MeCOCl and HMDS under the same reaction conditions (Table 4, Entry 4). The irreversible formation of amides in the reaction prompted us to investigate chiral alcohols. The 3CR of optically active alcohol **(*R*)-2g** with PhCOCl and HMDS afforded only racemic product **3ga** [Equation (1)], and this result suggest a carbocation intermediate[3b] is generated from the alcohol and/or its derivative(s) in the reaction.



(1)

Conclusions

We have disclosed a novel by-product-catalyzed three-component synthesis of amine derivatives using readily available benzylic and allylic alcohols as *N*-alkylating agents. In the absence of external catalysts and additives, the 3CR of benzylic (or allylic) alcohols with acyl chlorides (chloroformates or sulfonyl chlorides) and HMDS has been developed, for the first time, to produce the corresponding *N*-alkyl amides (carbamates or sulfonamides) in good to excellent yields. Furthermore, by-product TMSCl and its decomposition into HCl by an alcohol have been found to be essential for the by-product-catalyzed 3CR to take place.

Experimental Section

General Procedure for the Survey of Solvents: See Table 1. To a stirred solution of PhCOCl (42.2 mg, 0.035 mL, 0.30 mmol) in solvent (0.25 mL) were added successively HMDS (48.4 mg, 0.063 mL, 0.30 mmol) and alcohol **2a** (52.5 mg, 0.25 mmol). The resulting mixture was stirred at room temperature for 22 h and then concentrated. The residue was purified by silica gel column chromatography, eluting with petroleum ether/chloroform/acetone (30:40:2), to give product **3aa**.

General Procedure for the Three-Component Synthesis of Amides, Carbamates and Sulfonamides: See Table 2. To a stirred solution of acyl chloride (chloroformate or sulfonyl chloride, 0.30 mmol) in acetonitrile (or dioxane, 0.25 mL) at room temperature were added successively HMDS (48.4 mg, 0.063 mL, 0.30 mmol) and alcohol **2** (0.25 mmol). The resulting mixture was stirred at the temperature indicated in Table 2 until no further transformation was observed by TLC analysis. The mixture was concentrated, and the residue was purified by silica gel column chromatography to give product **3**.

***N*-Alkylation of Amide 1a with Alcohol 2e:** A mixture of PhCOCl (42.2 mg, 0.035 mL, 0.30 mmol) and HMDS (48.4 mg, 0.063 mL, 0.30 mmol) was stirred at room temperature for 24 h, and then subjected to reduced pressure to remove TMSCl. To the resulting white solid (amide **1a**) were added successively acetonitrile (0.25 mL), alcohol **2e** (52.5 mg, 0.25 mmol), and TMSCl (32.6 mg, 0.038 mL, 0.30 mmol). The resulting mixture was stirred at 75 °C for 5 h, cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography, eluting with petroleum ether/chloroform/acetone (30:40:2), to give product **3ea** (72.5 mg, 93%).

General Procedure for the Three-Component Reactions: See Table 4. To a solution of PhCOCl (42.2 mg, 0.035 mL, 0.30 mmol) in acetonitrile (0.25 mL) at room temperature were added successively HMDS (48.4 mg, 0.063 mL, 0.30 mmol), substrate (0.25 mmol), and 2-propanol (if any, 18.0 mg, 0.023 mL, 0.30 mmol). The mixture was stirred at 75 °C for 5 h, cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography, eluting with petroleum ether/chloroform/acetone (30:40:2), to give product **3ea**.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data of products.

Acknowledgments

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[11] For examples on the Brønsted acid catalyzed substitution of alcohols with nitrogen nucleophiles, see refs.[3c,3d,3h,3k,3q]

[12] $R^3NH(TMS)$ was monitored by TLC analysis. Due to its lability to moisture, the TMS group of $R^3NH(TMS)$ was removed on a TLC plate.

[13] Ether **4e** was isolated and identified by ^1H NMR analysis. The treatment of alcohol **2e** with TMSCl also resulted in the formation of ether **4e**.

[14] Silyl ether **5e** was not observed by TLC and ^1H NMR analysis.

[15] For an example of using molecular sieves to scavenge HCl, see: L. M. Weinstock, S. Karady, F. E. Roberts, A. M. Hoinowski, G. S. Brenner, T. B. K. Lee, W. C. Lumma, M. Sletzinger, *Tetrahedron Lett.* **1975**, *16*, 3979–3982. For details, see the Supporting Information.

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