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Reductive N-Alkylation of Amides, Carbamates and Ureas

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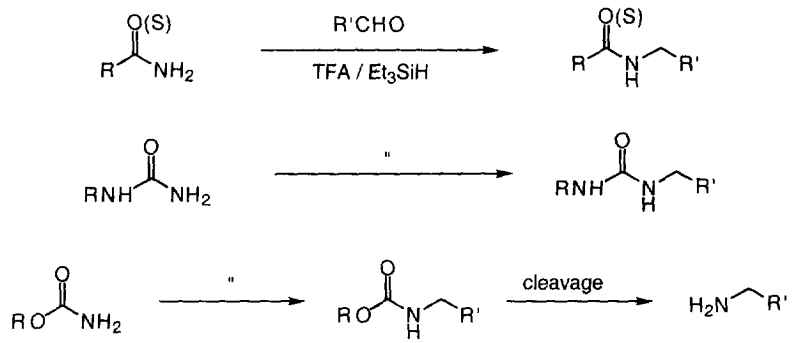
Abstract: A one pot selective mono N-alkylation of primary amides, thioamides, carbamates and ureas has been developed using aromatic and aliphatic aldehydes as alkylating agents and trifluoroacetic acid / triethylsilane as reagents. Application to an efficient synthesis of a primary amine from the corresponding aldehyde via the carbamate intermediate is presented.

The reductive N-alkylation of amides represent a possible complement to the more conventional approaches toward amide bond formation. Despite the apparent simplicity of the transformation there are few efficient methods currently available for mono N-alkylation of amides and related compounds.[1-3] Selective monoalkylation of amide is also possible under pressure of H_2 with Pd on carbon.[4] Weinreb *et al.*[5] have reported the reductive N-alkylation of amides using TFA / Et_3SiH [6] with formaldehyde as alkylating agent in a two step sequence. Reductive N-alkylation of a carbamate is also a potentially efficient way to obtain a primary amine directly from an aldehyde after deprotection (Scheme 1).

Herein, we disclose a practical procedure that uses a variety of aldehydes (aromatic and aliphatic), amides (aromatic and aliphatic) and other analogs like thioamides, carbamates and ureas to give mono N-alkylated products in good yields. This protocol is also readily applicable to rapid analog synthesis either in solution or on solid support because aqueous work up is not necessary and reagents can be evaporated.

Scheme 1



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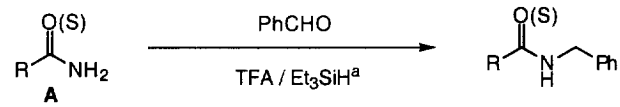
Among the solvents tested (acetic acid, acetonitrile, benzene, dichloromethane, 1,2-dichloroethane, methanol, THF and toluene) acetonitrile and toluene in most cases afforded the best isolated yields. The optimum amount of reagents was determined to be 3 equivalents of Et_3SiH and between 2 to 3 equivalents of TFA. The reaction goes to completion in a reasonable time frame (12-36 h) if an excess of either the amide or the aldehyde is used (3:1 ratio). Table 1 shows that the reaction is general for aliphatic (entry **1**) or aromatic amides (entry **2-4**) and is insensitive to *p*-substitution on the aromatic ring (entry **3-4**). Thiobenzamide (entry **5**), aromatic and aliphatic carbamate (entry **6-8**) or the corresponding ureas (entry **9,10**) gave similar yields. The ureas and carbamates are mono N-alkylated at room temperature and the reaction progresses fastest in acetonitrile. If higher temperature is used with the ureas then acylation of the primary amine (to give $RNHCONHCOCF_3$) can be a competitive process. The reaction failed with a strongly deactivated amide like trifluoroacetamide. Since either the aldehyde or the amide might be the limiting reactant, we have optimized the reaction conditions for both possibilities (Table 1).

Table 1 Reductive N-alkylation of amides, thioamides, carbamates and ureas with benzaldehyde

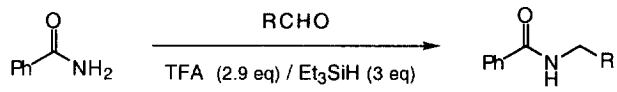


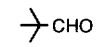
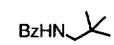
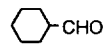
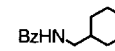
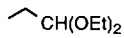
Entry	A	Solvent	T°C (Time)	Isolated Yield[b] (ratio A : PhCHO) 3 : 1	1 : 3
1	$PhCH_2CONH_2$	toluene	120 (36 h)	92 %	68 %
2	$PhCONH_2$	toluene	120 (18 h)	91%	94 %
3	4-F-$PhCONH_2$	toluene	120 (18 h)	92%	93 %
4	4-MeO-$PhCONH_2$	toluene	120 (18 h)	95%	91 %
5	$PhCSNH_2$	toluene	120 (36 h)	87%	63 %
6	$PhOCONH_2$	MeCN	22 (18 h)	90 %	85 %
7	$BnOCONH_2$	MeCN	22 (18 h)	95 %	92 %
8	t-$BuOCONH_2$	MeCN	22 (18 h)	92 %	81 %
9	$PhNHCONH_2$	toluene	22 (18 h)	92 %	97 %
10	$BnNHCONH_2$	toluene	22 (18 h)	89 %	88 %

(a) TFA 2.9 eq, Et_3SiH 3.0 eq (b) Yield based on the limiting reactant

Aliphatic aldehydes were investigated as well (Table 2). Primary, secondary or tertiary aldehydes gave results similar (≥90% yield) to aromatic aldehydes (entry **11-13**). Interestingly one can use acetals instead of aldehydes to obtain the corresponding mono N-alkylated product (entry **14**) in good yield. [7]

Table 2 Reductive N-alkylation of benzamide with various aliphatic aldehydes and an acetal

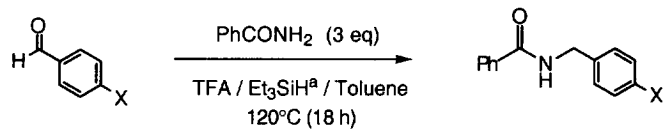


entry	R	Solvent	T°C (Time)	Product	Isolated Yield
11		Toluene	120 (18 h)		90%[a]
12		Toluene	120 (18 h)		92%[a]
13	MeCHO	MeCN	22 (18 h)	BzHNEt	95%[b]
14		MeCN	22 (18 h)	BzHNPr	65%[b]

(a) Yield based on aldehyde (b) Yield based on benzamide

We also studied the stability of various common functional and protective groups under the most demanding reaction conditions (toluene, 120°C). Acid, ester, fluorine or a hydroxyl group protected as an acetate, benzyl ether or t-butyldiphenylsilyl ether survived well under the reaction conditions (Table 3). Only the t-butyldimethylsilyl group was partially cleaved (entry **19**).

Table 3 Reductive N-alkylation of benzamide with *p*-substituted benzaldehydes

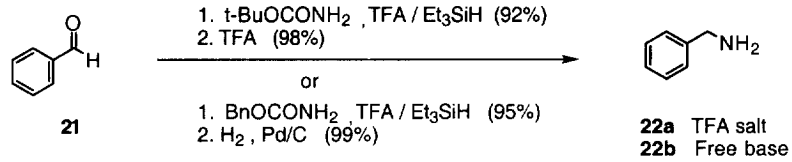


entry	X	Isolated Yield
14	F	96 %
15	CO_2Me	91%
16	CO_2H	96%
17	OAc	75%
18	OBn	90%
19	OTBS	46 %
20	OTBDPS	91%

(a) TFA (2.9 eq), Et_3SiH (3 eq)

Since t-butoxy (BOC) or benzyloxy (CBz) groups are easily removable protective groups, the present methodology can also be considered as a useful procedure to the synthesis of primary amines. After reductive N-alkylation with $BOCNH_2$ or $CBzNH_2$, the products are treated with Pd/C to remove the CBz or with TFA to remove the BOC group as demonstrated in the synthesis of benzylamine (**22**) (Scheme 2).

Scheme 2



21

22a TFA salt
22b Free base

In conclusion, we have described a methodology that enables a one pot selective monoalkylation of amides, thioamides, carbamate and ureas with various aromatics and aliphatic aldehydes covering a wide range of substitutions. Efficient synthesis of primary amines is possible via reductive N-alkylation of a carbamate followed by deprotection.

Typical experimental procedures:

Synthesis of N-benzyl benzamide: To a suspension of benzamide (722 mg, 5.91 mmol) in toluene (8 mL) was added benzaldehyde (200 µL, 1.97 mmol) followed by triethylsilane (950 µL, 5.91 mmol) and trifluoroacetic acid (450 µL, 5.79 mmol). The resulting reaction mixture was stirred at reflux for 18 hours and the solvent was removed in vacuo. The residue was purified by flash chromatography to afford N-benzyl-benzamide (381 mg, 91%) as a white solid. mp. 106-107 °C.

Synthesis of benzylamine: A solution of benzaldehyde (500 mg, 4.7 mmol), benzylcarbamate (2.1 g, 13.9 mmol) or t-butylcarbamate (1.6 g, 13.7 mmol), Et_3SiH (2.2 mL, 13.8 mmol), TFA (700 µL, 9.1 mmol) in CH_3CN (20 mL) was stirred at 22°C for 18 h. The mixtures were diluted with Et_2O, washed with $NaHCO_3$ sol. and brine. The organic layer was dried and the solvents evaporated. Purification by flash chromatography furnished the pure carbamates; CBzNHBn (1.08g, 95%) and BOCNHBn (895 mg, 92%) as white solids. To the N-CBz derivative in EtOAc was added Pd/C (10%, 20 mg) and the reaction placed under H_2 (balloon) for 18 h. Filtration on Celite and evaporation gave benzylamine (99%). To the N-BOC derivative was added TFA (3 mL) and the reaction mixture was stirred at 22°C for 15 min. The excess TFA was evaporated and the residue stirred in hexane-Et_2O then filtered to give benzylamine-TFA salt as a white solid (98%).

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References and Notes:

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