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LETTERS

Direct conversion of azides to carbamates and sulfonamides using Fe/NH_4Cl: effect of sonication[†]

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Abstract

A simple, direct and effective conversion of azides to carbamates and sulfonamides is achieved using Fe/NH_4Cl in methanol. The influence of sonication and direct application in solution phase combinatorial chemistry are also studied by developing a 6×4 matrix library. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: azides; carbamates; sulfonamides; sonication; combinatorial chemistry; iron.

Introduction of amino groups via reduction of an azido functionality[1] is carried out rather routinely in organic synthesis. Among the most common methods used for this transformation are hydride reagents,[2] catalytic hydrogenation[3] and metal acid reduction.[4] There are, however, very limited protocols available for direct conversion of azides to protected amines[5], which include Pd–C,[6] 20% Degussa $Pd(OH)_2/Et_3SiH$,[7] n-Bu_3P,[8] Me_3P,[9,10] in combination with $(Boc)_2O$ or alkylchloroformate. All these procedures suffer from their own disadvantages, for example, catalytic hydrogenation is not favored for substrates which contain the N–Cbz group or unsaturation, whereas phosphorus reagents are not recommended for aromatic azides and also result in unwanted byproducts.

Our own interest in the total synthesis of biologically significant molecules containing the amino[11] moiety in general demanded development of newer methodologies for the introduction of an amino group. Herein, we disclose our findings where Fe in combination with NH_4Cl and MeOH under the influence of sonication reduced azides to amines, which were insitu trapped with electrophiles viz., ClCOOEt, CbzCl, $(Boc)_2O$, TsCl and $PhSO_2Cl$ (Scheme 1). The versatility of this methodology was further demonstrated by directly converting azides to carbamates and sulfonamides in a combinatorial fashion (6×4 matrix) in a single operation in a sonicator for the first time. Sonication[12] has proved its efficiency in rate enhancement as well as yield

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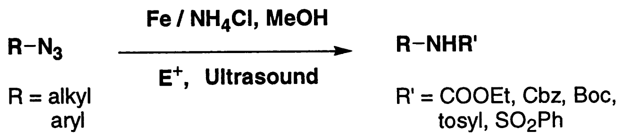
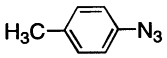
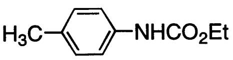
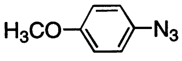
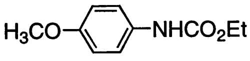
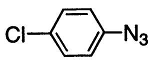
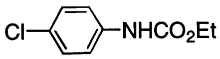
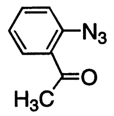
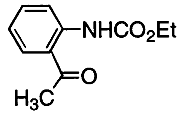
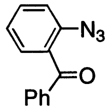
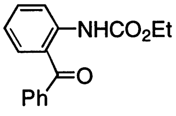
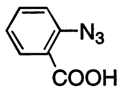
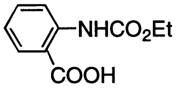
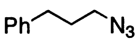
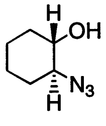
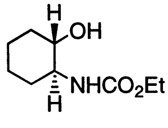
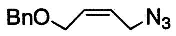
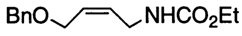
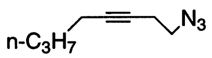
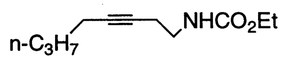


Scheme 1.

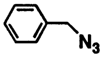
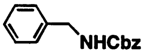
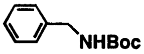
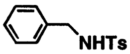
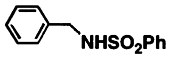
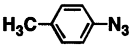
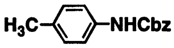
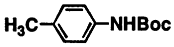
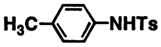
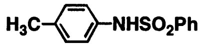
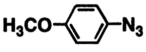
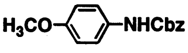
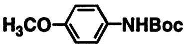
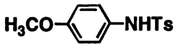
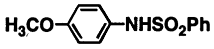
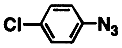
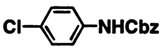
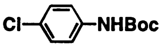
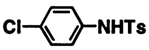
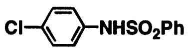
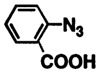
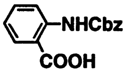
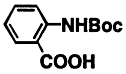
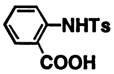
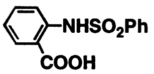
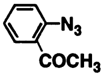
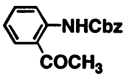
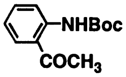
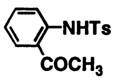
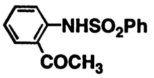
improvement and has a distinct advantage over microwave irradiation, which performs a similar function through rapid heating and which may not be desirable in some cases where the substrates are thermally labile. The efficiency of sonication may be attributed to chemical activation through cavitation. Initially benzyl azide (entry 1, Table 1) was subjected to reduction

Table 1

Entry	Substrate	Electrophile	Product	Condition Time / Yield (%)
1		$ClCO_2Et$		A: 15mins / 90 B: 12hrs / 65
2		$ClCO_2Et$		A: 30mins / 92 B: 9hrs / 67
3		$ClCO_2Et$		A: 30mins / 87 B: 12hrs / 63
4		$ClCO_2Et$		A: 15mins / 95 B: 9hrs / 71
5		$ClCO_2Et$		A: 45mins / 89 B: 12hrs / 68
6		$ClCO_2Et$		A: 60mins / 82 B: 12hrs / 60
7		$ClCO_2Et$		A: 30mins / 91 B: 9hrs / 72
8		$ClCO_2Et$		A: 45mins / 87 B: 12hrs / 55
9		$ClCO_2Et$		A: 60mins / 85 B: 12hrs / 62
10		$ClCO_2Et$		A: 30mins / 93 B: 12hrs / 66
11		$ClCO_2Et$		A: 30mins / 86 B: 12hrs / 59

Condition A : Sonication; Condition B: conventional heating (reflux)

Table 2

	CbzCl	Yield %	$(Boc)_2O$	Yield %	TsCl	Yield %	$PhSO_2Cl$	Yield %
		89		85		92		90
		87		82		90		88
		85		81		89		84
		90		83		91		87
		82		77		85		82
		78		75		81		79

with Fe/NH_4Cl in the presence of ethylchloroformate and MeOH as solvent to observe formation of *N*-carbethoxybenzylamine in 60% yield after refluxing for 12 h. Interestingly, however, when the same experiment was carried out in a sonicator,[13] the product was obtained in 90% yield within 15 min. Encouraged by this finding, other azido substrates (Table 1) were subjected to both conventional heating as well as sonication at 25°C and comparative time taken versus yield were recorded. In all the cases studied, without exception, all substrates behaved exceedingly well under the influence of sonication. For instance, *p*-chloroazidobenzene (entry 4), 2-azidoketones (entries 5,6), which contain hydride labile groups, yielded the corresponding carbamates in excellent yields. Similarly, hydrogenation sensitive substrates (entries 10 and 11) also yielded required carbamates without affecting the benzyl ether group, olefinic and acetylenic functionalities.

To further demonstrate the usefulness of the above methodology, the experiment was carried out in a combinatorial fashion (6×4 matrix). Various azides (Table 2, *y*-axis) were taken in 24 test tubes and were treated with CbzCl, $(Boc)_2O$, TsCl and $PhSO_2Cl$ (*x*-axis) in the presence of Fe/NH_4Cl and MeOH as solvent under sonication. After 1 h all the reactions were worked up by filtering and the products were obtained in excellent yields and high purity (>90%) after column chromatography.[14]

In conclusion, sonication has been utilized for efficient conversion of azides to amino derivatives in one pot using Fe–NH_4Cl. Also, its utility is further demonstrated by synthesizing a combinatorial library for the first time in a sonicator.

Acknowledgements

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13. A representative procedure: a mixture of benzyl azide (1 mmol), ethylchloroformate (1.1 mmol) iron powder (3 mmol) and NH_4Cl (5 mmol) in methanol (5 mL) was sonicated at 25°C. The progress of the reaction was monitored by TLC. At the end of the reaction the contents were filtered, washed with ethyl acetate (3×5 mL), the filtrate was dried (sodium sulfate) the volatiles removed and the crude material was chromatographed on silica gel to yield *N*-carbethoxybenzylamine in 90% yield.
14. All the products gave satisfactory spectral and analytical data.