

Indium-mediated efficient conversion of azides to carbamates†

Jhillu S. Yadav,* Basi V. Subba Reddy and Garudammagari S. Kiran Kumar Reddy

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India. Fax: +91 40 717 0512; E-mail: yadav@iict.ap.nic.in

Received (in Montpellier, France) 4th April 2000, Accepted 8th June 2000

Published on the Web 13th July 2000

A novel and efficient method for the high yield preparation of carbamates by the reaction of azides with several chloroformates using indium metal in DMF at ambient temperature is described for the first time.

Azides are an important class of compounds, particularly for producing primary amines *via* reductive transformation. Protection of amines with appropriate groups plays an important role in multistep synthesis of complex natural products and also in peptide synthesis. Among the various amine-protecting groups,¹ carbamates are commonly used due to their chemical stability towards acids, bases and hydrogenation. In addition to this, carbamates are well-known in the field of medicine and agrochemicals.² The most commonly used procedures for the conversion of azides to carbamates are based on the azide catalytic reduction, followed by *in situ* protection with Boc₂O.³ However, in spite of its potential utility, catalytic hydrogenation⁴ is generally incompatible with carbon–carbon multiple bonds, benzyloxycarbonyl (CBz) and related protecting groups present in the substrate. An alternative method for catalytic hydrogenation is the treatment of the azide with phosphines, followed by the reaction with Boc₂O⁵ or chloroformates.⁶ Some of these methods suffer from drawbacks like unsatisfactory yields with secondary/aromatic azides⁷ and require tedious isolation procedures to remove by-products.⁸ Even though catalytic hydrogenation and Staudinger methods have been employed for the direct conversion of azides to carbamates, such an organometallic reaction has not been hitherto applied for the preparation of carbamates. In recent years, indium-mediated reactions⁹ have received considerable attention due to its exceptional stability to air and water, compared to other metals. Since indium has special properties in organometallic chemistry, the application of indium for the one-pot conversion of azides to carbamates is of interest.

In continuation of our work on the applications¹⁰ of indium, zinc and magnesium for various transformations, herein we report a novel, convenient and practical method for the direct conversion of azides to carbamates using indium metal under mild reaction conditions (see Scheme 1). Thus, several aryl and alkyl azides (see Table 1) were converted into the corresponding carbamates by the reaction of the azide with equimolar quantities of the chloroformate and indium metal in DMF at room temperature. The application of this method to a variety of azides indicates the scope of the reac-

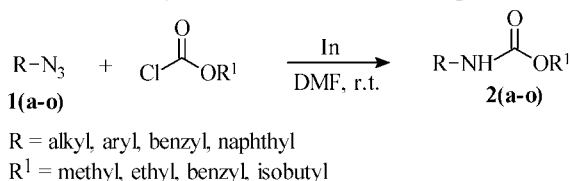
tion. The reaction proceeds smoothly at room temperature and does not require any promoter, stringent conditions or anhydrous solvent. The reaction of azides with chloroformates in the presence of indium is rapid and affords high yields of carbamates in a short time. All the products were characterized by ¹H NMR, IR and mass spectra. A variety of functional groups like esters, ethers, olefins, nitros and cyanos present in the substrate are unaffected under the reaction conditions. It should be emphasized that in the absence of indium, the reaction did not proceed and mainly resulted in the recovery of the starting materials. Similarly, the reaction of azides with Boc₂O in the presence of metals did not yield the product, even after a long reaction time at room temperature. The failure of this reaction with Boc₂O in the presence of indium metal clearly indicates that the chloroformate activates the metal, allowing the reaction to proceed rapidly at room temperature. Even though we have not studied the reaction mechanism in detail we presume that indium metal quickly reacts with chloroformates to generate an In(III) organometallic species that attacks the azide with loss of N₂ gas to afford an R–N(In)–COOR¹ intermediate, which on hydrolysis gave the desired carbamate. In the blank experiment the azides were not reduced by indium metal under the reaction conditions. The reaction was successful only with chloroformates in the presence of metals. Furthermore, high yields of products were isolated when the reactions were carried out in DMF. Among various metals like Mg, Zn and Sn used for this transformation, indium is found to be more effective than the others. The comparative yields of carbamates with zinc have also been summarized in the table.

In conclusion, this letter describes a novel, efficient and practical methodology for the high yield preparation of carbamates from azides using indium metal under mild conditions. The adopted procedure is very simple, rapid and convenient, and is a useful addition to the existing methods.

Experimental

A mixture of chloroformate (6 mmol) and activated indium or zinc powder (6 mmol) was stirred in commercial dimethyl formamide (10 ml) for 5 min at 0 °C. A solution of azide (5 mmol) in commercial DMF (5 ml) was then slowly added and the mixture stirred for an appropriate length of time at room temperature. After complete conversion, as indicated by TLC, the reaction was quenched with aqueous ammonium chloride (20%, 20 ml) and extracted with ether (2 × 25 ml). The combined organic layer was washed with brine (20 ml), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to yield crude product, which was purified by column chromatography on silica gel (Aldrich, 100–200 mesh, ethyl acetate–hexane 1 : 9), to afford pure carbamate.

2c: ¹H NMR (CDCl₃): δ 1.4 (t, 3H, *J* = 7.8 Hz), 2.3 (s, 3H), 4.3 (q, 2H, *J* = 7.8 Hz), 6.4 (br s, NH), 7.4–7.65 (m, 3H). IR (KBr): ν_{max} 3288 (NH), 1690 (CO), 2982, 1577, 1528, 1479,



Scheme 1

† IICT Communication No. 4465

Table 1 Indium-mediated one-pot conversion of azides to carbamates

Entry	Azide	Chloroformate	Carbamate	Reaction time/min ^a	Yield (%) ^b
a				30(90)	90(83)
b				45(120)	88(75)
c				60(80)	95(87)
d				55(70)	87(81)
e				40(60)	91(78)
f				35(85)	85(75)
g				25(50)	78(70)
h				35(65)	71(68)
i				60(85)	86(76)
j				30(60)	90(87)
k				20(45)	87(74)
l				25(75)	83(65)
m				30(80)	72(63)
n				30(55)	83(77)
o				45(70)	81(68)

^a Reaction times of the corresponding zinc-mediated reaction are given in parentheses. ^b Reaction yields of the corresponding zinc-mediated reaction are given in parentheses.

1440, 1390 cm⁻¹. MS: VG micromass 7070 (70 eV) *m/z* (%) 257 [M]⁺ (40), 259 [M]⁺ (40), 184 [m - COOEt]⁺ (30), 103 (100), 75 (50), 47 (35).

Acknowledgements

BVS thanks CSIR, New Delhi, for the award of a fellowship.

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