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CONVENIENT METHOD FOR N-DEBENZYLATION OF TERTIARY AMINES

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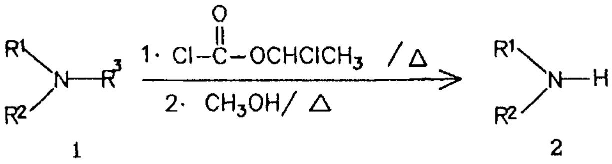
Abstract: N-Benzyl tertiary amines on reaction with ethyl chloroformate give the corresponding debenzylated N-carbamates which on treatment with $I_3B{:}N(C_2H_5)_2Ph$ complex yield the secondary amines.

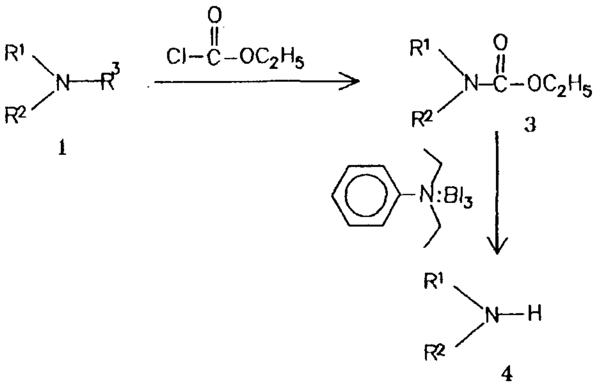
The N-debenzylation of tertiary amines is usually carried out using $Pd/C/H_2$ or under catalytic transfer hydrogenation conditions ($Pd/C/NH_4^+HCOO^-$).[1] A new process involving the use of α-chloroethyl chloroformate has been reported for the selective N-dealkylation of tertiary amines (Scheme 1).[2,3]

Scheme 1



In the course of our efforts towards the preparation and utilization of chiral amine–borane complexes,[4,5] we were looking for a method for the N-debenzylation of tertiary amines utilizing relatively less expensive reagents. We wish to report that this can be achieved utilizing the inexpensive ethyl chloroformate and the readily accessible $I_3B{:}N(C_2H_5)_2Ph$ complex (Scheme 2).

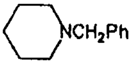
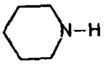
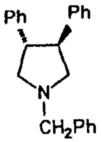
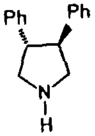
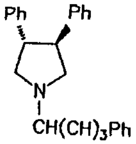
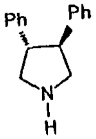
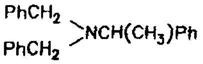
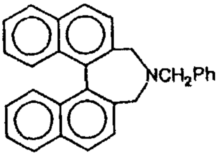
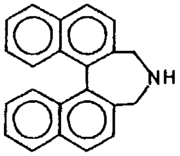
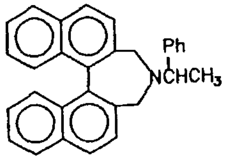
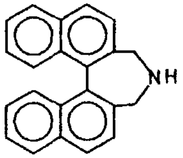
Scheme 2



The N-benzyl and N-α-methylbenzylamine derivatives (Table 1) are readily converted to the corresponding N-carbamates by adding chloroformate (1.1 eq) to the amine in dichloroethane at 25°C and then refluxing the mixture for the time mentioned in Table 1.

We have observed that the N-carbamate of the 3, 4- diphenylpyrrolidine is resistant to alkaline hydrolysis even under relatively harsh conditions (10N KOH/CH_3OH reflux, 72h) and gives the secondary amine only in 30% yield besides unreacted starting material. However, the conversion can be readily effected at 25°C using the readily accessible $I_3B{:}N(C_2H_5)_2Ph$.[6]

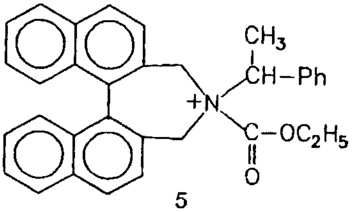
Table:N-Debenzylation of tertiary amines[a].

S. No.	Substrate	Reaction time(h)[b]		Product	Yield(%)[c]
		1–3	3–4		
1.		12	8		80
2.		4	8		89
3.		4	8		88
4.	 $(PhCH_2)_2NCH(CH_3)Ph$	20	8	$(PhCH_2)_2NH$	87
5.		8[d]	8		85
6.		8[d]	8		87

(a). All reactions were carried out in 5 mmol scale. (b). The transformation 1–3 (Scheme 2) was carried out in refluxing dichloroethane. The conversion of 3–4 (Scheme 2) was carried out at 25°C. (C). Yields are of isolated and purified products. Products were identified by spectral data (IR, ^{1}H NMR and ^{13}C NMR) and comparision with the data reported in literature. (d). Mass spectral data were also obtained for these samples.

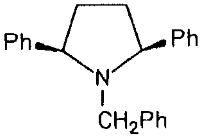
The α-methylbenzyl group is cleaved in preference to benzyl group as exemplified in the case of N- α-methy l benzyl dibenzylamine (entry no.4, Table 1). Also, in the cyclic derivatives containing binaphthyl moiety (entry no.s 5 and 6, Table 1), the N-benzyl and N-α-methylbenzyl groups are cleaved leaving the ring intact.

The diasteriomeric tertiary amine starting materials (entry no. 6, Table 1) can be readily prepared through the reaction of chiral α-methylbenzylamine with the corresponding dibromide.[5] Unfortunately, these separated optically pure substances give the corresponding racemic N-carbamate on treatment with ethyl chloroformate under the reaction conditions. Presumably, the racemisation takes place because of the intermediacy of quaternary nitrogen (5) during this transformation. Such cyclic quaternary derivatives have been reported to undergo racemisation.[7]

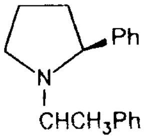


5

The N-benzyl-2,5-diphenylpyrrolidine (6) and N-α-metyl benzyl-2-phenylpyrrolidine (7) did not react with ethyl chloroformate even after refluxing 48 h in dichloroethane. Presumably, the formation of the quaternary salt similar to 5 is difficult in these cases.



6



7

Several reports have appeared on the utilization of the $I_3B:N(C_2H_5)_2Ph$ complex following our initial report on the preparation and utilization of the complex.[8-12] We have demonstrated here the ability of this useful $I_3B:N(C_2H_5)_2Ph$ reagent to cleave N-carbamates.

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(6) Representative procedure for debenzylation: To a solution of diasteriomerically pure (+)N-α-methylbenzyl-3,4-diphenyl pyrrolidine (1.63g, 5 mmol) in dry dichloroethane (20 ml), ethyl

chloroformate (0.66g, 6 mmol) was added and the mixture was refluxed for 4h. The solvent was removed under reduced pressure to yield essentially pure N-ethyl carbamate derivative. Yield: 1.4g, (95%). IR(neat): 1680, 1600 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$): δ ppm 1.2 (t, 3H), 3.4-4.2 (m, 8H), 7.1 (m, 10H). ^{13}C NMR (25.0 MHz, $CDCl_3$): δ ppm 14.6, 50.4, 51.3, 53.1, 60.9, 126.9, 127.4, 128.5, 139.2, 154.9.

N,N-Diethylaniline-BI_3 complex was prepared following the reported procedure,[8] through the addition of I_2(7.5 mmol) in benzene to N,N-diethylaniline borane complex (5 mmol) and stirring the mixture at 25°C for 8h. To this, the N-ethyl carbamate of 3,4-diphenylpyrrolidine(1.47g, 5 mmol) in benzene (20 ml) was added slowly during 15 min. under nitrogen and the mixture was stirred further for 8h. The reaction was quenched with water and neutralised using 3N NaOH solution. The organic layer was separated and washed with NaOH solution (3N, 3x10 ml), brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded crude product which was separated from N,N-diethylaniline by column chromatography on alumina (neutral) using hexane : ethyl acetate/80:20. Yield: 0.95g, (89%). IR(neat): 3345, 1600 cm^{-1}. ^1H NMR(100 MHz, $CDCl_3$): 2.3 (s, 1H), 2.8-3.4 (m, 6H), 6.9 (m, 10H). $[\alpha]_D^{20} = +222^\circ$(C1, $CHCl_3$). *Lit.* $[\alpha]_D^{20} = -226^\circ$($CHCl_3$). Tomioka, K., Nakagima, M. and Koga, K. *Chemistry Lett.*, 1987, 65.

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