Reaction of *O*-Benzyl-*N*-methylenehydroxylamine with Organolithium Compounds, a CH_2^+–NH^+ Synthetic Equivalent

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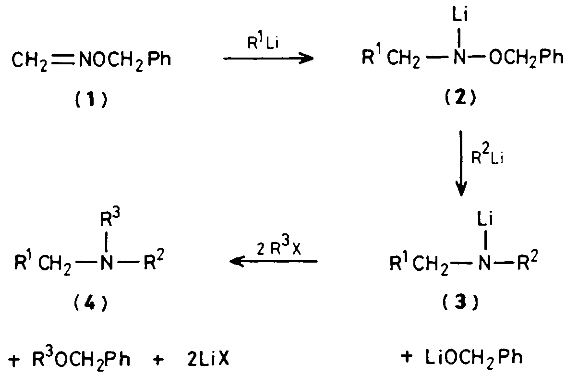
Lithium carbanions add sequentially to *O*-benzyl-*N*-methylenehydroxylamine (**1**), first at the electrophilic carbon and subsequently, at higher temperature, on the nitrogen with concomitant loss of the benzyloxy group, resulting in a CH_2^+–NH^+ synthetic equivalent, the amines (**4**) being produced.

We demonstrate the use of *O*-benzyl-*N*-methylenehydroxylamine (**1**)[1] as a reagent which exhibits electrophilic character at carbon and, depending upon the choice of reaction conditions, either electrophilic or nucleophilic character at nitrogen. This reagent can thus be used as a CH_2^+–N^-OCH_2Ph or CH_2^+–NH^+ synthetic equivalent. An organolithium reagent first adds to the electrophilic carbon and subsequently, at higher temperature, to the negatively charged nitrogen intermediate (**2**) with concomitant displacement of the benzyloxy group providing the lithium amide intermediate (**3**) which in reactions with various electrophiles gives adducts of the type (**4**) as shown in Scheme 1.

Treatment of a solution of the imine (**1**) in tetrahydrofuran with n-butyl-lithium (1 equiv.) at −40 °C for 5 min followed by quenching with aqueous saturated $NH_4^+Cl^-$, benzoyl chloride, or benzyl bromide provided the adducts $Bu^nCH_2NHOCH_2Ph$ (71%), $Bu^nCH_2N(COPh)OCH_2Ph$ (85%), and $Bu^nCH_2N(CH_2Ph)OCH_2Ph$ (42%), respectively. These examples illustrate the ready addition of an organolithium compound to the electrophilic carbon of the imine (**1**), and subsequent quenching of the proposed intermediate (**2**) with various electrophiles such as acyl halides and alkyl halides proceeds smoothly to provide the corresponding adduct.

Recently, Beak and co-workers[2] have reported that alkoxyamines can be used to aminate organolithium compounds. Busch and Hobien reported the displacement of a methoxy group in the reaction of $MeON{=}CH_2$ with phenylmagnesium bromide.[3] We have observed that the first equivalent of organolithium added rapidly to (**1**) at −40 °C, but that subsequent warming to 0—40 °C for 1—3 h was necessary for the addition of the second equivalent with concomitant displacement of the benzyloxy group generating the proposed intermediate lithium amide (**3**) which was quenched with an acyl chloride to provide the corresponding secondary amide



Scheme 1

(**4**) according to Scheme 1. Since the first addition of organolithium proceeded rapidly at −40 °C and displacement of the benzyloxy group from the negatively charged nitrogen did not occur to an appreciable extent at this temperature, the sequential addition of two different organolithium reagents to the imine (**1**) was possible. The results of typical examples where (**1**) is serving as a CH_2^+–NH^+ synthon are summarized in Table 1.† Treatment of (**1**) with methyl-lithium for 30 min at 0 °C provided $PhCH_2ON(Et)CH_2NHOCH_2Ph$ exclusively.

The reactions of the imine (**1**) thus provide efficient access to various *N*-benzyloxyamines and derivatives thereof. Since methods[4] exist for the conversion of *N*-benzyloxyamines into the corresponding hydroxylamines (H_2, Pd/C) or amines (Zn, HCl), (**1**) can also be used as a CH_2^+–NROH or a CH_2^+–NRH synthon (R = alkyl or H). The *N*-benzyloxyamides are readily converted into the corresponding hydroxamic acid or amide.

Table 1. Reaction of the imine (**1**) to give the adduct (**4**).[a]

R^1	R^2	R^3X	% Yield of (**4**)
Ph	Ph	*p*-$MeOC_6H_4COCl$	37
Bu^n	Bu^n	PhCOCl	70
Bu^n	Ph	*p*-PhC_6H_4COCl	47
Bu^s	Bu^n	*p*-$MeOC_6H_4COCl$	50
Bu^n	Bu^n	$PhCH_2Br$	25

[a] All compounds (liquids) were characterised by elemental analysis, mass and n.m.r. spectroscopy (300 MHz).

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† A representative procedure is as follows. To the imine (**1**) (0.88 mmol) dissolved in dry ether (5 ml) and cooled to −40 °C under nitrogen was added n-butyl-lithium (2.5 M in hexane; 1.76 mmol). The mixture was allowed to warm to 0 °C for 1 h and a solution of benzoyl chloride (1.76 mmol) in tetrahydrofuran (5 ml) was then added. The mixture was stirred at 25 °C for 6 h; aqueous Na_2CO_3 (5 ml) and dichloromethane (20 ml) were then added. The organic layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which was purified by chromatography (silica gel, 20% ether in pentane) resulting in (152 mg, 70% yield) $Bu^nCH_2N(Bu^n)COPh$.