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ORGANOMETALLIC REACTIONS OF α-HALOIMINES AS A USEFUL TOOL IN ORGANIC SYNTHESIS

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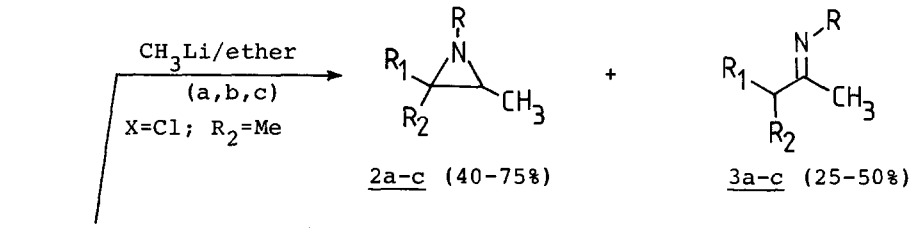
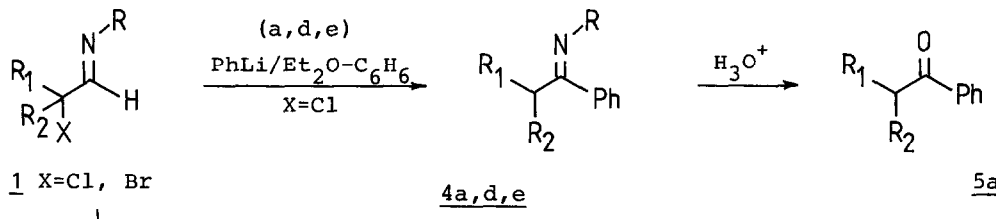
Abstract : The reaction of organometallic reagents, e.g. alkyllithiums, cuprates and alkylcoppers, with α-haloimines gave selectively a variety of synthetically useful reactions, including coupling to 1,4-diimines, homologation, and production of heterocycles.

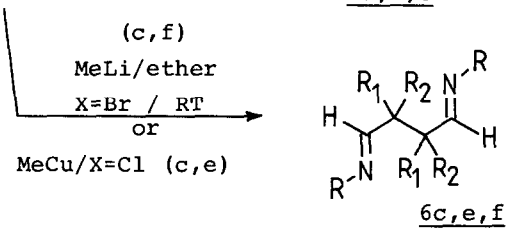
The use of α-haloimines as synthons in organic chemistry is of fairly recent origin, but it has already been shown that their chemistry deviates markedly from that of the corresponding oxygen analogues, i.e. α-halo-carbonyl compounds.[2]

There is very little published work on the reactivity of α-haloimines towards organometallic reagents;[2] however, a recent report[3] on the reaction of α-halo-oxime ethers with organometallics to afford coupled products prompts us to disclose our preliminary results in this field.

The reaction of tertiary α-chloroaldimines 1, bearing at least one α-methyl substituent, with methyllithium (2 equiv.) in ether under reflux (1.5 hr) gave rise to a mixture of aziridines 2 and the homologated methylketimines 3.[4] When no α-methyl group was present, e.g. 1e (R_1=R_2=Et; X=Cl) no aziridine was formed and the homologation was the sole reaction. A similar exclusive homologation was noticed with phenyllithium and α-chloroaldimines 1a,d,e. As an example, N-(2-chloro-2-ethyl-1-butylidene)isopropylamine 1e (X=Cl) was converted with phenyllithium in ether/benzene (3:7) under reflux (1 hr) into N-(2-ethyl-1-phenyl-1-butylidene)isopropylamine 4e, which was hydrolyzed with aqueous acid into 2-ethylbutyrophenone 5e (72% overall yield).[4] This trans-



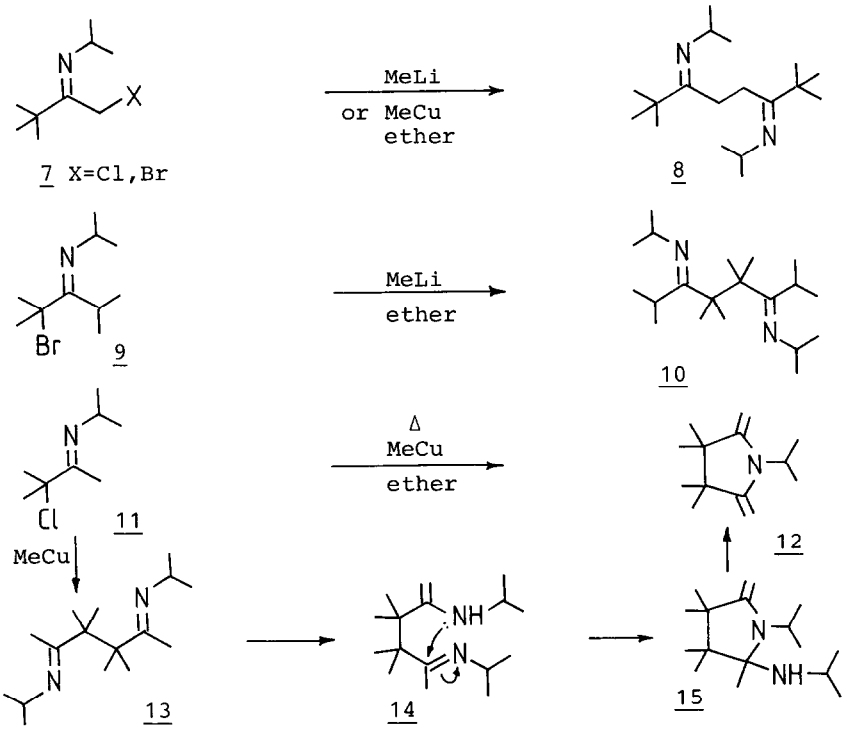




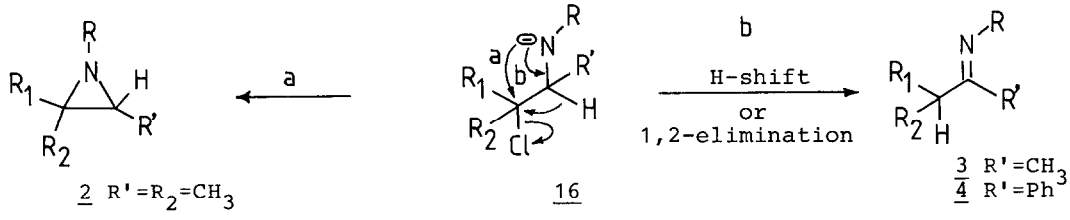
	a	b	c	d	e	f
R	iPr	iPr	tBu	cHex	iPr	tBu
R_1	Me	Et	Me	Me	Et	$(CH_2)_5$
R_2	Me	Me	Me	Me	Et	

formation represents a useful and mild acylation of arenes under non-Friedel-Crafts conditions. On the other hand, tertiary α-chloroaldimines 1c,e with methylcopper in ether (15 hr reflux) afforded 1,4-diimines 6c,e, exclusively (85-89%).[4,5] The same coupling products 6 were obtained when tertiary α-bromoaldimines 1c,f (X=Br) were reacted with methyllithium, methylcopper or lithium dimethylcuprate in ether. All of the last three reagents converted α-bromoaldimine 1f (X=Br), into spiro diimine 6f in 90-100% yield. α,α-Dichloroaldimines, e.g. 1 (R_1=Et, R_2=X=Cl, R=iPr) with methyllithium in ether (0°, 30 min) gave mainly α-methylation (79%), affording α-monochloroaldimine 1 (R_1=Et, R_2=Me, X=Cl, R=iPr). Also α-haloketimines were subject to coupling reactions with organometallic reagents. Primary[8] as well as tertiary α-haloketimines 7 and 9 with methyllithium, methylcopper or lithium dimethylcuprate, could be converted cleanly into 1,4-diimines 8 and 10 in high yield (86-100%).[4] Simple hydrolysis with aqueous oxalic acid provides an easy access to 1,4-diketones. In the case of N-(3-chloro-3-methyl-2-butylidene)isopropylamine 11, the 1,4-diimine 13, formed by coupling with methylcopper in ether, could not be isolated but underwent intramolecular condensation to ge-

nerate the bis-methylenepyrrolidine 12.[9]



The mechanism of the reactions discussed in this paper can be classified into two main categories. Those reagents (e.g. methyllithium) which add across the imino bond of aldimines afford an adduct 16, which either undergoes



intramolecular nucleophilic substitution (route a) to give aziridines 2 or might give an hydride shift (route b) or simple dehydrochlorination to afford homologation products 3 and 4. Those substrates which are not liable to adduct formation undergo a coupling reaction to 1,4-diimines which can be understood in terms of a radical process, but alternative ionic reactions might be operative as well. At present no proof can be forwarded in favor of one or another process but work is under way to elucidate this mechanism.

References

1. N. De Kimpe : "Bevoegdverklaard Navorser" (Research Associate) of the Belgian "Nationaal Fonds voor Wetenschappelijk Onderzoek". This is part 33 of our series on the chemistry of α-halogenated imines.

2. For review articles on α-haloimine chemistry, see : N. De Kimpe et al., Org. Prep. Proced. Int., 12, 49 (1980); N. De Kimpe, R. Verhé in "The Chemistry of Halides, Pseudo-halides and Azides (Supplement D), Ed. S. Patai and Z. Rappoport, J. Wiley & Sons, Chapter 13, pp. 549-601 (1983).

3. S. Shatzmiller, R. Lidor, Synthesis 590 (1983).

4. All new compounds gave spectrometric (^{1}H and ^{13}C NMR, IR, MS) and analytical data in full agreement with the proposed structure.

5. A coupling reaction of α-haloaldimines to form 1,4-diimines and pyrroles has been previously observed with lithium or sodium metal[6] and Grignard reagents.[6a,7]

6a. P. Duhamel, L. Duhamel, J.-Y. Valnot, Tetrahedron Letters, 1339 (1973).

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7. N. De Kimpe, R. Verhé, L. De Buyck, H. Hasma, N. Schamp, Tetrahedron, 32, 2457 (1976).

8. For a related coupling reaction see : M. Larchevêque, G. Valette, T. Cuvigny, H. Normant, Synthesis 256 (1975).

9. Compound 10 (mp 143°C) : ^{1}H NMR ($CDCl_3$); 1.10(12H,d,J=6Hz,2xNC$\underline{Me}_2$), 1.16 (12H,s,2x$\underline{Me}_2$), 1.22(12H,d,J=7Hz,2xN=C-CH$\underline{Me}_2$), 2.94(2H,septet,J=7Hz,2xCHC=N), 4.22(2H,septet,J=6Hz,2xNC$\underline{H}$). IR (KBr) : 1638 cm^{-1} ($\nu_{C=N}$). ^{13}C NMR ($CDCl_3$): 21.29(q,$\underline{Me}_2$C), 23.90(q,$\underline{Me}_2$C-N), 25.22(q,$\underline{Me}_2$CHC=N), 31.16(s,$\underline{C}Me_2$), 49.53 and 49.68(each d,N$\underline{C}$H and $\underline{C}$HC=N), 175.06(s,$\underline{C}$=N). MS : 308(M^+; 1%), 70(100%). Compound 12 : ^{1}H NMR ($CDCl_3$) : 0.97(12H,s,Me_4), 1.32(6H,d,J=7Hz,Me_2), 4.00 (1H,septet,J=7Hz,NC$\underline{H}$), 3.73 and 3.83(each 1H,AB,J=2Hz,C=$\underline{C}H_2$). ^{13}C NMR ($CDCl_3$) : 17.77(q,Me_2), 22.74(q,Me_4), 44.93(s,$\underline{C}Me_2$), 45.28(d,N$\underline{C}$H), 74.58(t, $\underline{C}H_2$=C), 158.19(s,$\underline{C}$=CH_2). IR (NaCl) : 1640 cm^{-1} ($\nu_{C=C}$). MS : 193(M^+; 32%), 178(100%).

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