Sodium Diphenylketyl Alkylation by Chiral Electrophilic Reagents

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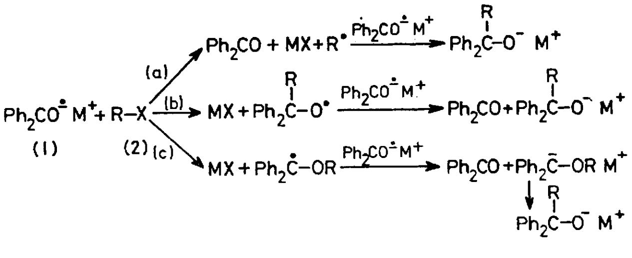
Summary Sodium diphenylketyl reacts with 1-methylheptyl bromide and mesylate with partial inversion of configuration; these results agree with a mechanism involving S_N2 and electron transfer reactions in competition.

Three mechanistic pathways have been proposed for the alkylation of alkali metal diphenylketyls: electron transfer followed by radical combination (Scheme 1, a), an S_N2-like process with direct alkylation of carbon (b), or alkylation of oxygen followed by Wittig rearrangement (c).[1]



Scheme 1

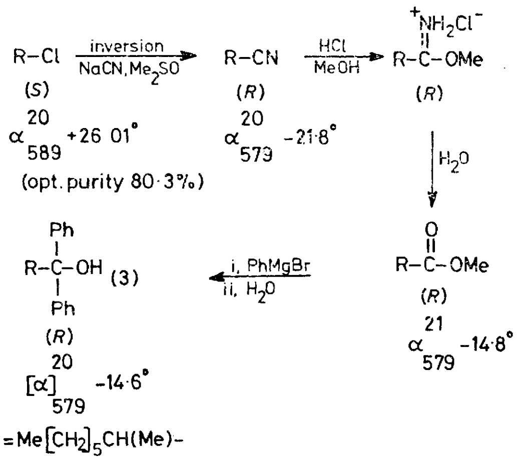
Recently, Garst *et al.*[1] reported that for lithium diphenylketyl (**1**; M = Li), the main pathway is electron transfer (Scheme 1, a) but for other alkali metals, an S_N2 process might also be considered. We now report preliminary results on the reaction of sodium diphenylketyl (**1**; M = Na) with optically active electrophiles (**2**; R = 1-methylheptyl; X = Br or OSO_2Me). The reactions of (**2**) (10 mmol) [absolute configurations (*R*) and (*S*) for X = Br and OSO_2Me, respectively with optical purities 62 and 85%†] with (**1**; M = Na) (25 mmol) in tetrahydrofuran (THF) (100 cm^3), give the products (**3**) and (**4**) in approximately equal amounts.‡ The product (**4**) results from alkylation at one phenyl ring, followed by aromatization on contact with air.[1,2] The obtention of similar products has been reported before.[1–3]

$Ph_2C(OH)CH(Me)[CH_2]_5Me$ (**3**) $\quad$ *p*-$Me[CH_2]_5CH(Me)C_6H_4COPh$ (**4**)

The products (**3**) obtained from the (+)(*S*)-mesylate and (−)(*R*)-bromide have optical rotations $[\alpha]^{25}_{579}$ −4·6° and +0·8°,§ respectively.

In order to determine the absolute configuration of (**3**), we have prepared it by the stereochemically unambiguous sequence in Scheme 2.

Comparison of the rotation of compound (**3**) obtained in the two different reactions demonstrates that substitution of R–X by sodium diphenylketyl occurs with partial inversion of configuration. Assuming that in the sequence in Scheme 2 racemization does not occur,¶ optically pure (**3**) has $[\alpha]^{20}_{579}$ 18·20°; the calculated inversion is therefore *ca.* 5% with the bromide and 25% with the mesylate.** These results are comparable to the previously reported partial inversion of configuration obtained with lithium anthracenylide,[4] and may be accounted for by dual pathways involving electron transfer and S_N2 substitution.



Scheme 2

Alternative pathways have already been considered.[4] The intermediacy of benzophenone dianion due to the dismutation equilibrium $2Ph_2\dot{C}O^-Na^+ \rightleftharpoons Ph_2CO^{2-}2Na^+ + Ph_2CO$, could be responsible of the inversion of configuration. Another pathway, as suggested by one of the referees, is reaction of $Ph_2\dot{C}O^-M^+$ with an intermediate RX radical anion; the mesylate radical anion should be the more stable, so the maximum inversion should be observed in this case. However these paths do not agree with the reported[1] overall second-order kinetics (first order in diphenylketyl).

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† 1-Methylheptyl mesylate was obtained from (+)(*S*)-octan-2-ol, α^{20}_D +5·08°; optical purity, 62·4%; 1-methylheptylbromide has α^{20}_D −37·73°; optical purity 85% (H. M. R. Hoffmann, *J. Chem. Soc.*, 1964, 1249).

‡ Sodium diphenylketyl was prepared by direct reaction between benzophenone and metallic sodium in anhydrous THF. After addition of RX, the solution was stirred for 4 h at 20 °C under dry N_2. Subsequent hydrolysis with H_2O led to the alkylated compounds (**3**) and (**4**) in 30—50% yield, which were isolated by preparative t.l.c. and g.l.c. I.r., n.m.r., and mass spectra and analysis were consistent with the assigned structures.

§ The optical rotations were determined in benzene, on a Perkin Elmer polarimeter, with a 1 dm cell. There was no concentration effect on the [α] values. The values −4·6° and +0·8° were calculated with respect to use of optically pure samples of mesylate and bromide.

¶ This is a reasonable assumption because reactions of NaCN in Me_2SO involve S_N2 processes (C. M. Starks, *J. Amer. Chem. Soc.*, 1971, **93**, 195; R. A. Smiley and C. Arnold, *J. Org. Chem.*, 1960, **25**, 257) and CN^- is much more a nucleophilic than a basic reagent. Unfortunately there is no experimental proof of the absence of racemization of octane-2-nitriles having an acidic α hydrogen. Optically active 2-methyloctanoic acid has been reported but its optical activity was only estimated (R. L. Letsinger, *J. Amer. Chem. Soc.*, 1950, **72**, 4842; A. Rothen and P. A. Levene, *J. Chem. Phys.*, 1939, **7**, 975).

** The extent of the contribution of the inversion of configuration is less certain. In another experiment with mesylate, 32% inversion was observed, but experiments with increased reaction times (20 instead of 4 h) led to contradictory results: 10% inversion was obtained for bromide, but for mesylate the compound (**3**) obtained was almost completely racemic. This variation in results could be due to partial racemization of the organometallic intermediate $Ph_2C\text{-}(R)O^-Na^+$ in the reaction mixture before hydrolysis. This question is under investigation.

[1] J. F. Garst and C. D. Smith, *J. Amer. Chem. Soc.*, 1976, **98**, 1520.
[2] M. I. Mostova, D. V. Ioffé, and I. L. Malko, *Zhur. org. Khim.*, 1976, **12**, 2580; M. I. Mostova and D. V. Ioffé, *ibid.*, 1972, **8**, 1547.
[3] R. Turle and J. G. Smith, *Tetrahedron Letters*, 1968, **27**, 2227; J. G. Smith and R. A. Turle, *J. Org. Chem.*, 1972, **37**, 126; G. O. Schenk and G. Mathias, *Tetrahedron Letters*, 1967, 699.
[4] M. Malissard, J. P. Mazaleyrat, and Z. Welvart, *J. Amer. Chem. Soc.*, in the press.