Utilization of the Deuterium Isotope Effect to suppress Enolization during Alkylation of Ketones

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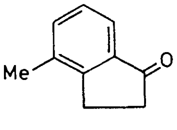
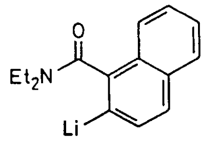
Summary A substantial enhancement in yield is observed in the reaction of enolizable ketones with the lithium salts of *N*,*N*-diethylbenzamide and *N*,*N*-diethyl-1-naphthamide when the hydrogen atoms α to the carbonyl group are replaced with deuterium.

Synthesis of the potent carcinogen 3-methylcholanthrene (3-MC) *via* a synthetic approach involving in the key step condensation of 4-methylindan-1-one (**1**) with 2-lithio-*N*,*N*-diethyl-1-naphthamide (**2**) has recently been described.[1] The moderate yield (30%) of the lactone intermediate (**3**) was assumed to be a consequence of enolization of the ketone, since analogous reactions of non-enolizable aryl aldehydes afforded much higher yields.

In order to test the possibility that the enolization pathway could be partially suppressed through replacement of the α-hydrogen atoms of (**1**) with deuterium, we prepared 2,2-dideuterio-(**1**) from (**1**) by K_2CO_3-catalysed exchange with deuteriomethanol. Reaction of the deuteriated ketone with (**2**) under identical conditions gave the expected lactone in substantially improved yield (52%).† Analogous reactions of 2-lithio-*N*,*N*-diethylbenzamide with 2,3-dihydrophenalen-1-one (**4**) and its α,α-dideuteriated analogue furnished the expected products in yields of 22 and 50%, respectively.‡



(1)



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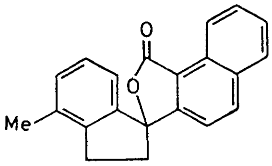

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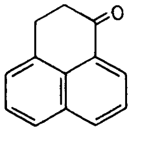

(4)

These results indicate that deuteriation can substantially enhance the yields of alkylation of enolizable ketones. These are the first examples, to our knowledge, of this relatively dramatic effect. Recently Miyano has utilized the deuterium isotope effect to direct dehydration of steroidal alcohols regioselectively to *endo*-olefins.[2]

The deuterium atoms can be retained or replaced with hydrogen as desired. In the synthesis of 3-MC, reduction of the synthetic intermediate 1,1-dideuterio-6-acetoxy-3-MC with hydriodic acid in propionic acid with a short reaction time gave 1,1-dideuterio-3-MC, while prolonged treatment with the acid furnished 3-MC.

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† The 270 MHz ^{1}H n.m.r. spectrum of the deuteriated lactone closely matched that of (**3**) except for the absence of one pair of methylene protons at δ 2·6—2·9 and the decreased complexity of the splitting pattern of the remaining methylene protons.

‡ In these cases the lactones were reduced with zinc and alkali[1] to the corresponding carboxylic acids which gave satisfactory elemental analysis data; the n.m.r. spectra were also in agreement with the assigned structures.

[1] S. A. Jacobs and R. G. Harvey, *Tetrahedron Lett.*, 1981, **22**, 1093.
[2] M. Miyano, *J. Org. Chem.*, 1981, **46**, 1854.