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1,2- VERSUS 1,4-ADDITION REACTIONS OF LITHIOMETHYLNITROGENOUS HETEROCYCLES WITH α,β-UNSATURATED KETONES[1]

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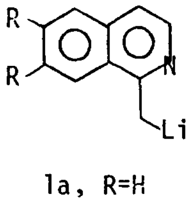
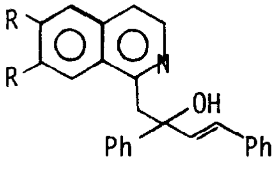
The interaction of carbanions with various α,β-unsaturated ketones has long been known to afford alcohols and/or saturated ketones derived from 1,2- and/or 1,4-addition reactions, respectively.[2] More recent papers have discussed the reversibility of such reactions in terms of thermodynamic versus kinetic control. For example, alkaliphosphonate esters have been found to add 1,4 kinetically and 1,2 thermodynamically to benzylideneacetone.[3] In contrast, certain lithiocyanohydrins,[4] lithiophenylacetonitrile,[5] various lithiocarboxylic acid esters,[6] and lithiodithianes[7] have been shown to add 1,2 kinetically but 1,4 thermodynamically to a large number of such compounds. This paper discloses that lithium salts stabilized only by nitrogenous heterocycles similarly add to α,β-unsaturated ketones by reversible 1,2-kinetically controlled reactions and by 1,4-thermodynamically controlled additions. Moreover, a method is described which prevents reversion of some or all of the less stable 1,2-alkoxide adduct intermediates to more stable ones.

Thus, 1-(lithiomethyl)isoquinoline (1a) and chalcone in THF afford mostly the 1,2-adduct 2a[8] (54%) at -78° and the 1,4-adduct 3a (72%) at 25°. Similar results were realized with 6,7-dimethoxy-1-(lithiomethyl)isoquinoline (1b) and chalcone to give more 2b at both -78° and 25°, but mostly 3b at 60°. That the 1,2-adducts are formed via kinetically controlled processes was demonstrated by the conversion of 2b to 3b at 60° by means of a catalytic amount (0.15 equiv.) of *n*-butyllithium.



1a, R=H
1b, R=OCH$_3$



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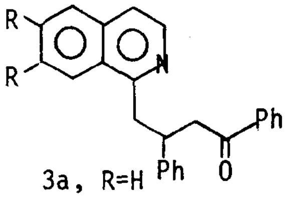
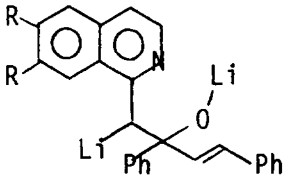
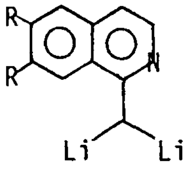


3a, R=H
3b, R=OCH$_3$

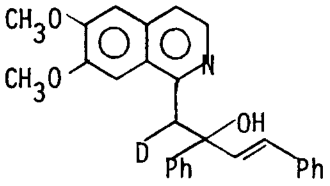
Interestingly, when 1a was prepared in the presence of an extra equivalent of lithium diisopropylamide (LDIPA) and chalcone then added even at 25°, more 1,2-adduct 2a (34%) was obtained than 1,4-adduct 3a (14%). A similar result was realized with 1b and this ketone. The success of the extra equivalent of base in affording more of what appears to be the kinetically controlled products under conditions of higher temperature which should lead to thermodynamically controlled ones may be ascribed to the formation of dianions 4a,b. Such dianions would preclude reversion to carbanions and chalcone since the resulting di-charged compounds 5a,b would be sufficiently basic to be relatively poor leaving groups. Evidence for the formation of 4b was obtained by trapping this species with deuterium oxide to give 6. Incidentally, even if 4a,b were to revert to 5a,b and chalcone, the latter carbanions should be "harder" than 1a,b and would thus be expected to react with the ketone under charge control, i.e., at the carbonyl carbon rather than at the β-carbon.[3] gem-Dilithio salts 5a,b are presumably not present initially in such reactions before chalcone is added since deuteration of 1b in the presence of an extra equivalent of LDIPA but in the absence of the ketone gave recovered parent heterocycle containing only one deuterium atom on the methyl side-chain.



4a, R=H
4b, R=OCH_3



5a, R=H
5b, R=OCH_3



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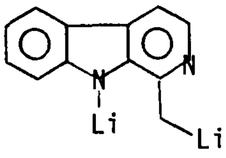
Among other related lithio salts added to such ketones, dilithioharman (7) has likewise been condensed with chalcone to afford mostly 1,2-adduct 8 at -78° and 1,4-adduct 9 at 25°. Interestingly, when 7 and chalcone were heated to 60°, 1,2-adduct 8 was again obtained, but without the previously necessary extra equivalent of base. Possibly, an internal acid-base reaction occurs which converts intermediate 10 to doubly-chelated 11 or to a compound with substantial negative charge on the 1-methylene side-chain. We have been unable to trap an intermediate in this reaction to date. As above, 11 or a related material is believed to prevent reversion to carbanion and the α,β-unsaturated ketone.

Similar results have been observed with α,β-unsaturated ketones other than chalcone. For example, 1 and 12 afford 1,4-adduct 13 (86%) at 25° and 1,2-adduct 14 (59%) at 60°; the latter reaction was effected with excess LIDPA. On the other hand, 1 and ketone 15 have yielded only 1,4-adduct 16 under all conditions studied to date including -78° and the use of excess basic reagents. These results confirm that such reactions are subject to steric effects by substituents across a ring from the unsaturated carbonyl functional group. Earlier, lithiophenyl-



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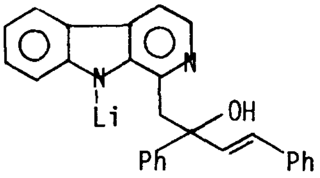

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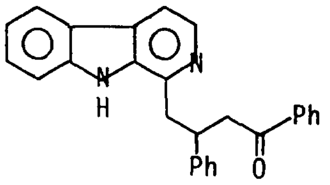

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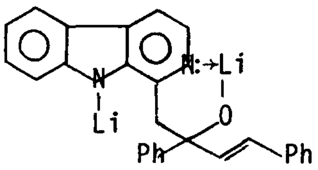

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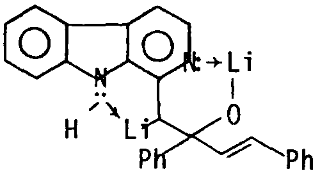

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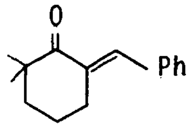
acetonitrile had been shown to add both 1,2 and 1,4 to 3-methylcyclohex-2-enone, but only 1,4 to more sterically hindered 3,5,5-trimethylcyclohex-2-enone.[5] Parenthetically, the ^{13}C NMR spectrum[9] of 14 indicates that this compound is better described as the alcohol shown below rather than the previously suggested quinolizinium hydroxide salt.[10]



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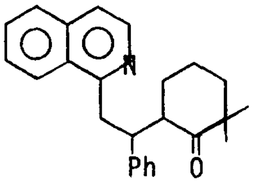

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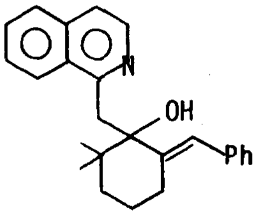

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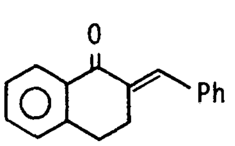

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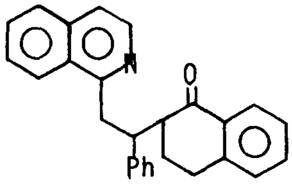

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A broad study is in progress to determine the generality of such addition reactions of lithiomethylnitrogenous heterocycles with a wide variety of α,β-unsaturated systems.

Summary of Yields of 1,2- and 1,4-Adducts

Anion	Ketone	Temp.,°C	1,2-Adduct	%^{a}	1,4-Adduct	%^{a}
1a	Chalcone	-78°	2a	54	3a	25
	Chalcone	25	2a	Trace	3a	72
	Chalcone	25^b	2a	34	3a	14
	12	25	14	0	13	86
	12	60^b	14	59	13	0
	15	-78	—	—	16	62
	15	25^b	—	—	16	53
1b	Chalcone	-78	2b	36.5	3b	26.8
	Chalcone	25	2b	37.2	3b	19.5
	Chalcone	60	2b	Trace	3b	58.8
	Chalcone	60^b	2b	20.9	3b	29.2
7	Chalcone	-78	8	41	9	30.5
	Chalcone	25	8	0	9	80
	Chalcone	60	8	41	9	35.9

a. Material balances were generally excellent where the only other substances obtained were recovered starting materials.

b. The anion was prepared in the presence of an extra equivalent of base.

References

1. Supported by the National Institute of General Medical Sciences, National Institutes of Health on grant GM21500.
2. For example, see M.S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, 1954, pp. 196-238.
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5. R. Sauvetre and J. Seyden-Penne, Tetrahedron Lett., 3949 (1976).
6. A.G. Schultz and Y. K. Lee, J. Org. Chem., 41, 4044 (1976).
7. P.C. Ostrowski and V.V. Kane, Tetrahedron Lett., 3549 (1977).
8. The structures of the products were supported by elemental analysis and by IR and NMR spectroscopy.
9. We thank Professor Richard N. Loeppky for determining the spectra; full disclosure will be made later.
10. E.M. Kaiser and P.L. Knutson, Tetrahedron Lett., 3583 (1975).