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SYNTHESIS OF 3-ARYL-3,4-DIHYDROISOCARBOSTYRILS BY CONDENSATION OF LITHIATED N,N-DIETHYL-O-TOLUAMIDES WITH BENZALDIMINES[1]

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Abstract - The cyclocondensation of lithiated N,N-diethyl-o-toluamide (1) with benzaldimines (2) at -70°C gave directly 2-alkyl-3-aryl-3,4-dihydroisocarbostyrils (3) in 37-50% yield.

The synthesis of 3-aryl-3,4-dihydroisocarbostyrils (3) using conventional methodology would be expected to involve multistep, and often low-yielding, reaction sequences.[2,3] Our interest in a direct route to this class of compounds prompted us to investigate the reaction of lithiated N,N-diethyl-o-toluamide (1)[4] with benzaldimines (2). We now report that this reaction furnishes 2-alkyl-3-aryl-3,4-dihydroisocarbostyrils (3) in one step, albeit in modest yield. The results of a number of these cyclocondensations are given in the Table.

In a typical procedure, a THF solution of 1 equiv. of N,N-diethyl-o-toluamide was added to 1 equiv. of lithium diisopropylamide in THF at -70°C. The resulting dark purple solution of 1 was then treated with a THF solution of imine 2 (1.2 equiv.) and the dark mixture was then stirred at -70°C for 5-20 min.[5] The reaction mixture was quenched with dilute hydrochloric acid and the products were isolated by ether extraction and purified by silica gel chromatography (3a-d) or crystallization (3e). Although the yields of 3 are modest (37-48%), this is overcome somewhat by the simplicity of the process and by the fact that the crude products are relatively pure since the major by-products are basic materials which remain in the aqueous acidic layer upon workup.

The condensation can also be performed by adding a preformed solution of LDA to a -70°C solution of 1 and 2 in THF. In the case of imine 2c, the yield of 3c was improved somewhat (to 50%) using this modification.[6]

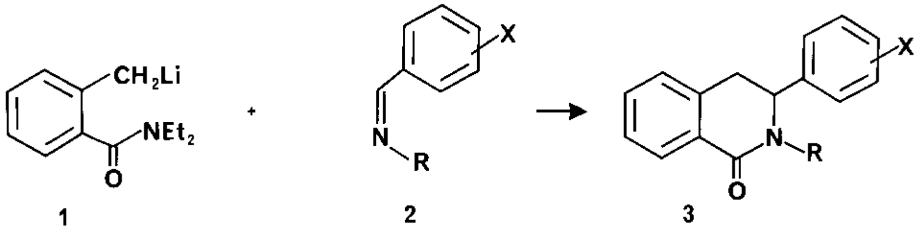


Table: 3,4-Dihydroisocarbostyrils from Condensation of 1 and 2

Imine	R	X	Product	Yield (%)[a,b]	M.P. (°C)
2a	cyclohexyl	4-OCH_3	3a	48	oil
2b	cyclohexyl	2-CH_3	3b	42	foam
2c	n-butyl	4-OCH_3	3c	42	oil
2d	CH_3	4-OCH_3	3d	37	98-99
2e	6,7-dimethoxy-3,4-dihydro-isoquinoline		3e[c]	43	138-139[d]

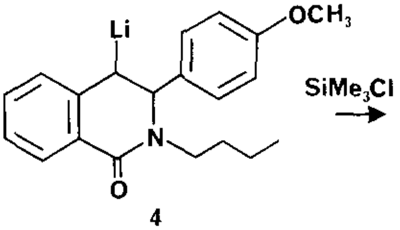
a) Compounds 3a-d were purified by silica gel chromatography (ethyl acetate/hexane). 3e was obtained by crystallization of the crude product from ethyl acetate/hexane.

b) Satisfactory IR and NMR spectra and combustion analyses were obtained for 3a-e. Representative spectral data for 3d is given in footnote 18.

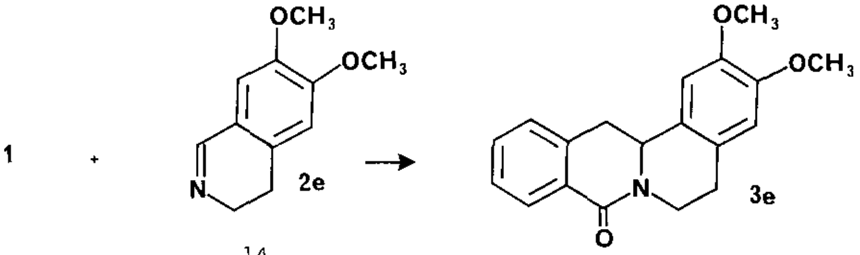
c) See structure in text.

d) Literature, mp 142°C (Reference 8). The NMR spectral data matched those reported in References 9 and 10.

It is important to keep the reaction temperature below -60°C since above this temperature 1 begins to self-condense. In addition, since the lithium dialkylamide base is regenerated in the cyclocondensation process, the product 3 is deprotonated under the reaction conditions to a 4-lithiated dihydroisocarbostyril (e.g. 4). This species undergoes a number of side reactions (such as ring opening to a stilbene) if the low temperature is not maintained. In one example, this lithiated dihydroisocarbostyril was trapped with trimethylsilyl chloride to afford 5[7] in 30% yield.



Reaction of the cyclic imine 6,7-dimethoxy-3,4-dihydroisoquinoline (2e) with 1 gave 2,3-dimethoxy-8-oxoberbine (3e).[8-10] A related synthesis in which lithiated phthalide was condensed with 2e to give 2,3-dimethoxy-13-hydroxy-8-oxoberbine has been reported.[11] Another similar transformation is the condensation of imines with homophthalic anhydrides.[12,13]



Lithiated o-toluic acid,[14] methyl o-toluate, and N-methyl-o-toluamide,[15] were also investigated in condensations with 2. *However, none of these* species led to production of dihydroisocarbostyrils. In the case of dilithiated N-methyl-o-toluamide, an adduct was formed which did not cyclize either upon workup or on heating at 150°C. This is in contrast to the reaction of this dilithio species with nitriles in which cyclization to 3-substituted isocarbostyrils occurs readily.[16] 3-Substituted isocarbostyrils have also been prepared by reaction of dilithiated N-methyl-o-toluamide with N,N-dimethylcarboxamides.[17]

The results presented herein demonstrate that the cyclocondensation of 1 and 2 affords a direct route to 3-aryl-3,4-dihydroisocarbostyrils (3). In addition, lithiated intermediates such as 4 may serve as useful synthetic intermediates.

ACKNOWLEDGEMENT

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4. The condensation of lithiated 6-methoxy-N,N-dimethyl-o-toluamide with aldehydes has been reported: P. Beak and V. Snieckus, Acc. Chem. Res., 1982, 15, 306.
5. Imines 2c-e condense with 1 almost immediately. The cyclohexylimines 2a-b were somewhat slower and in these cases a 20 min reaction time was employed.
6. The use of substantially less than 1 equiv. of LDA was also investigated. However, this did not lead to useful results.
7. 5: oil: IR (film) 1645 cm^{-1}; NMR ($CDCl_3$) δ 8.10 (m, 1H, H-8), 7.33-6.70 (m, 3H), 6.76 (AB, 4H), 4.76 (s, 1H, H-3), 3.90 (dt, 1H, NCH_a), 3.60 (s, 3H), 2.93 (dt, 1H, NCH_b), 2.45 (s, 1H, H-4), 1.80-1.00 (m, 4H), 0.92 (t, 3H), 0.05 (s, 9H). Anal. for $C_{23}H_{31}NO_2Si$: C,H,N.

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18. 3d: IR (KBr) 1650 cm^{-1}; NMR ($CDCl_3$) δ 8.10 (m, 1H, H-8), 7.33-6.50 (m, 6H), 4.67 (dd, J = 2.5, 5 Hz, 1H, H-3), 3.78 (s, 3H), 3.67 (s, 3H), 3.60 (dd, J = 5,12 Hz, H-4a), 3.05 (s, 3H), 2.93 (dd, J = 2.5, 12 Hz, H-4b).

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