Preparation and Condensations of 6,7-Dimethoxy-1-lithiomethylisoquinoline[1]

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Although the preparation of 1-lithiomethylisoquinoline (**1**) was first described twenty years ago[2], the literature seems devoid of references to the corresponding 6,7-dimethoxy derivative **2**. The organolithium compound **2** could prove to be a useful intermediate in synthetic methodology because of the large number of medically active compounds containing the 6,7-dimethoxy-1-isoquinolyl moiety[3]. This paper discusses a convenient preparation of **2** and its condensations with a variety of electrophiles. Moreover, the scope

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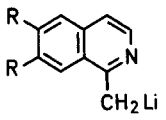
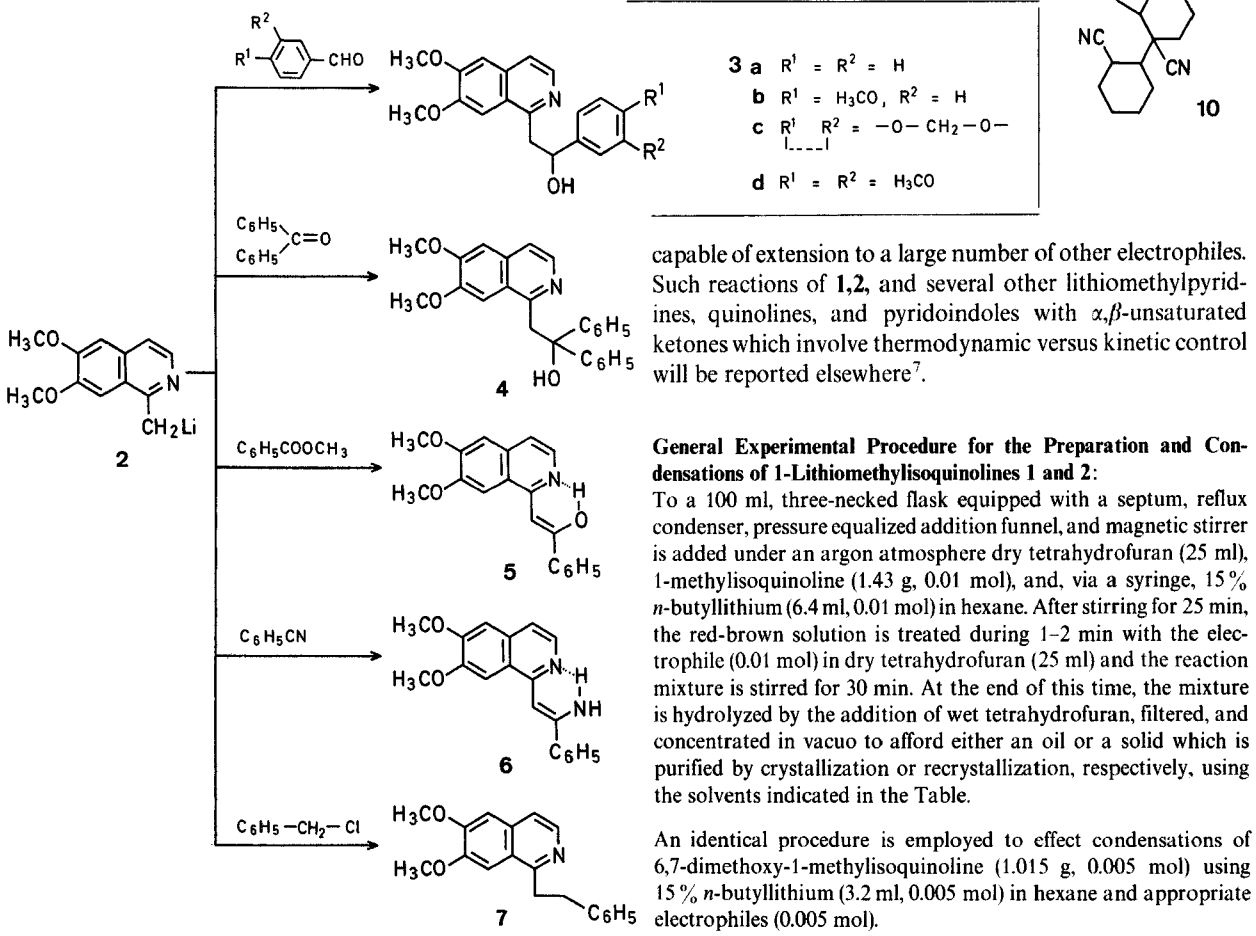
of reactions of **1** has been broadened to include a large number of aldehydes. Previously, **1** has been combined with several alkyl halides[2], esters[2,4], a few ketones[2,4,5], one nitrile[6], and α,β-unsaturated carbonyl compounds.



1 R = H
2 R = H_3CO

First, the lithium reagent **2**, easily synthesized from 6,7-dimethoxy-1-methylisoquinoline and *n*-butyllithium in tetrahydrofuran at 25°, was condensed with benzaldehyde, anisaldehyde, piperonal, and veratraldehyde to afford **3a–d**, respectively (69–96%). Of particular interest is the preparation of homopapaverinol **3d** (96%). Reagent **2** was also combined with other kinds of electrophiles illustrated by benzophenone to give alcohol **4** (78%), methyl benzoate to yield enol **5** (71%), benzonitrile to afford enamine **6** (85%), and benzyl chloride to give **7** (85%).

Isoquinoline reagent **1** itself was also condensed with the four aldehydes above to afford **8a–d** (66–91%), with *N*-methylisatin to give **9** (62%), and with 1-cyano-1-cyclohexene to yield **10** (42%). The yield of the latter compound was increased to 88% using the lithium thiophenylcuprate salt of **1**.



3 a $R^1 = R^2 = H$
b $R^1 = H_3CO$, $R^2 = H$
c R^1 R^2 = $-O-CH_2-O-$
d $R^1 = R^2 = H_3CO$

The structures of the above products were supported by microanalyses, and by N.M.R. and I.R. spectroscopy. These condensations of **1** and **2** seem general and should be capable of extension to a large number of other electrophiles. Such reactions of **1**,**2**, and several other lithiomethylpyridines, quinolines, and pyridoindoles with α,β-unsaturated ketones which involve thermodynamic versus kinetic control will be reported elsewhere[7].

General Experimental Procedure for the Preparation and Condensations of 1-Lithiomethylisoquinolines 1 and 2:

To a 100 ml, three-necked flask equipped with a septum, reflux condenser, pressure equalized addition funnel, and magnetic stirrer is added under an argon atmosphere dry tetrahydrofuran (25 ml), 1-methylisoquinoline (1.43 g, 0.01 mol), and, via a syringe, 15% *n*-butyllithium (6.4 ml, 0.01 mol) in hexane. After stirring for 25 min, the red-brown solution is treated during 1–2 min with the electrophile (0.01 mol) in dry tetrahydrofuran (25 ml) and the reaction mixture is stirred for 30 min. At the end of this time, the mixture is hydrolyzed by the addition of wet tetrahydrofuran, filtered, and concentrated in vacuo to afford either an oil or a solid which is purified by crystallization or recrystallization, respectively, using the solvents indicated in the Table.

An identical procedure is employed to effect condensations of 6,7-dimethoxy-1-methylisoquinoline (1.015 g, 0.005 mol) using 15% *n*-butyllithium (3.2 ml, 0.005 mol) in hexane and appropriate electrophiles (0.005 mol).

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[1] Supported by the National Institute of General Medical Sciences, National Institutes of Health on grant R01GM21500.

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Table. Products obtained from 1-Lithiomethylisoquinolines **1** and **2** and Electrophiles

Lithium compound	Electrophile	Product	Yield [%]	m.p.	Recrystallization solvent	Molecular formula[a]
2	benzaldehyde	**3a**	74	153–155°	benzene	$C_{19}H_{19}NO_3$ (309.4)
2	anisaldehyde	**3b**	86	119–121°	benzene/ether	$C_{20}H_{21}NO_4$ (339.4)
2	piperonal	**3c**	69	136–137°	ether	$C_{20}H_{19}NO_5$ (353.4)
2	veratraldehyde	**3d**	96	151–153°	benzene	$C_{21}H_{23}NO_5$ (369.4)
2	benzophenone	**4**	78	187–188°	chloroform/benzene	$C_{25}H_{23}NO_3$ (385.4)
2	methyl benzoate	**5**	71	174–177°[b]	ether/benzene	$C_{19}H_{17}NO_3$ (307.3)
2	benzonitrile	**6**	85	193–195°[c]	acetone	$C_{19}H_{18}N_2O_2$ (306.4)
2	benzyl chloride	**7**	85	104–106°[d]	ether	$C_{19}H_{19}NO_2$ (293.4)
1	benzaldehyde	**8a**	80	109–112°	benzene/ether	$C_{17}H_{15}NO_3$ (281.3)
1	anisaldehyde	**8b**	87	87–87.5°	benzene/ether	$C_{18}H_{17}NO_3$ (295.3)
1	piperonal	**8c**	66	72–75°	ether	$C_{18}H_{15}NO_3$ (293.3)
1	veratraldehyde	**8d**	91	112–114°	benzene/ether	$C_{19}H_{19}NO_3$ (309.4)
1	*N*-methylisatin	**9**	62	189–192°	ethanol	$C_{19}H_{16}N_2O_2$ (304.3)
1	1-cyanocyclohexene	**10**	42–88	147–149°[e]	acetone	$C_{24}H_{27}N_3$ (357.5)

[a] Each compound exhibited satisfactory microanalyses (±0.3%) for C, H, and N (Galbraith Laboratories, Knoxville, Tenn.); the I.R. and ^{1}H-N.M.R. spectra were consistent with the structure assigned.

[b] Hydrochloride, m.p. 180–182°; picrate, m.p. 260–265°.

[c] *N*-Acetyl derivative, m.p. 193–195°.

[d] Lit.[8] m.p. 103–105°.

[e] Hydrochloride, m.p. 255–257°.

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