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ULTRASOUND IN ORGANIC SYNTHESIS 10[1].
SELECTIVE ORTHO-LITHIATION OF THE BOUVEAULT REACTION INTERMEDIATE

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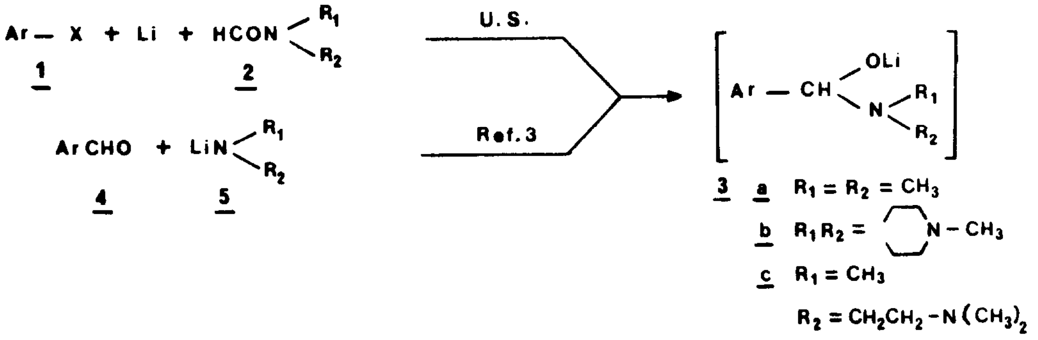
Summary : The Bouveault reaction intermediate prepared under sonochemical conditions easily undergoes orthodirected lithiation. The use of tetrahydropyran as a solvent dramatically increases the rates and yields of metallation which can be accomplished with an in situ generated alkyl-lithium.

In the preceding note[1] we report new data for the optimization of the Bouveault reaction which efficiently produces aldehydes from aromatic halides, lithium and several formamides under sonication. The intermediate α-amino-alkoxide 3 offers synthetic potentialities as the substituent of the ring contains hetero-atoms known to be effective in the regioselective orthometallation of the aromatic nucleus[2].
Examples of such reactions have recently been described by Comins et al[3] who prepare intermediates 3 by addition of a lithium amide 5 to an aldehyde.



As the Bouveault reaction permits a straightforward and easy access to amino-alkoxides 3, we investigated further improvements of the lithiation step.

Thus starting from bromobenzene, the corresponding compound 3 can be obtained as previously described by sonication in various solvents in the presence of lithium (2% Na) and DMF or amides 6 or 7. The reaction product in homogeneous solution is then allowed to react with an alkyl-lithium reagent and the resulting dianion treated with an electrophile (table 1).

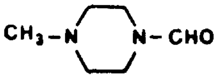
Table

Formation of 3 Conditions		Lithiation step Conditions	Condensation step Electrophile	Conditions	Product	Yield[a] %
3b	45 min 500 KHz in Et_2O	2.2 eq. nBuLi 15 h, R.T.	2.2 eq. 6	0°C	9a	40
		1.1 eq. nBuLi 1.1 eq. TMEDA 15 h, R.T.	1.5 eq. 6	-78°C	9a	traces
	10 min 50 KHz in THF	1.4 eq. n BuLi 24 h, R.T.	2 eq. DMF	0°C	9a	24
	10 min 50 KHz in THP	1.2 eq. nBuLi 3 h.	2 eq. DMF	0°C	9a	24
		1.5 h	3 eq. CH_3I	0°C	9b	16
		1.2 eq. tBuLi 1.5 h.	2 eq. DMF	0°C	9a	34
		0.75 h.	3 eq. CH_3I	0°C	9b	40
3c	30 min 500 KHz in Et_2O	1.1 eq. nBuLi 15 h, R.T.	1.5 eq. 6	0°C	9a	16
	10 min 50 KHz in THF	3 eq. n BuLi -30°, 24 h	3.5 eq. DMF	12 h -78°C ↗ R.T.	9a	17
	10 min 50 KHz in THP	1.2 eq. n BuLi 0.5 h, R.T.	2 eq. DMF	0°C	9a	62
		1.2 eq. sBuLi 0.25 h, 0°C	2 eq. DMF	0°C	9a	60
		1.2 eq. nBuLi 0.25 h, R.T.	3 eq. CH_3I	0°C	9b	62

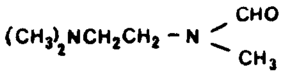
[a] VPC yields with hexadecane as internal standard

As DMF and formamides 6 and 7 were shown to be of equivalent efficiency in the Bouveault step[1], the higher yields obtained from 3b and 3c in comparison to 3a can be attributed to the presence of a supplementary nitrogen atom which improves the lithiation step. This metallation reaction however remains sluggish in diethylether and THF, and the alkyl-lithium has to be used in excess. Several attempts to improve the rate by addition of tetramethyl-ethylenediamine (TMEDA) revealed no advantage. A second observation relates to the considerable importance of the solvent for the success of the metallation. Tetrahydropyran is generally the appropriate medium for successfull transformations. In this solvent, a quasi stoichiometric amount of alkyl-lithium is sufficient for complete transformation. s-Butyl or t-Butyl-lithium reagents offer no decisive synthetic advantage.

As the results evidence that formamide 7 appears to be largely preferable to the other amides tested, the optimal conditions require then the sonication of 1.1 equiv. of this compound, 2.2 equiv. of lithium with 1 equiv. of bromobenzene in tetrahydropyran (2mL per mmole of ϕ Br) at 15-18°C for 15 min., to form 3c. n-Butyl-lithium (1.2 equiv) is then added at room temperature. Short reaction times, 15 - 30 min, are sufficient for best yields of dianion 8 which exhibits a slight tendency to decomposition under these conditions (2-5% per hour).

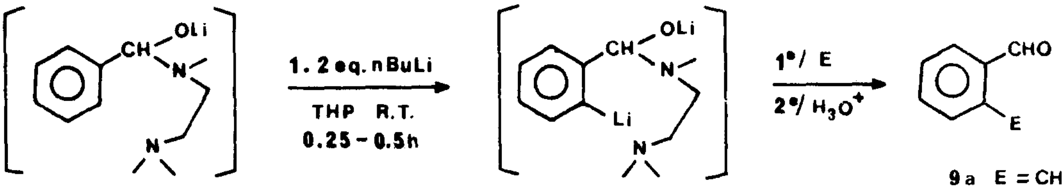


6



$(CH_3)_2NCH_2CH_2-N(CHO)(CH_3)$

7



3c

8

9a E = CHO

b E = CH$_3$

It is worth mentioning that previously described procedures[3] require large excess of metallating agent (3 equiv.), long reaction times and in some cases higher temperatures (refluxing benzene), to give generally lower yields. The efficiency of the procedure presented here is connected to the use of THP as a solvent. Analogously, Posner and Canella[4] succeeded in the orthometallation of lithium phenoxide in THP, but the reaction failed in other media.

Condensation of dianion 8 with DMF or methyl iodide gives phthalaldehyde 9a or o-tolualdehyde 9b. The overall yield of the sequence from bromobenzene is 62% in each case, which represents an average 85% yield for each individual step.

As the metalating species used in these reactions is an alkyl-lithium, we tried to improve the synthetic path by exploiting the possibility to generate the R-Li species in situ under the action of sonic waves. Thus, starting from bromobenzene, amide 7 and excess lithium (2% Na, Alfa) in THP, sonication for 15 min. lead to a quasi quantitative conversion to intermediate 3 as checked by VPC.

Metallation was then effected by dropwise addition in 15 min. of 1.2 equiv. of n-butyl bromide instead of n-BuLi, under sonication, followed by 30 min. stirring at room temperature. Excess (3 equiv.) of methyl iodide was then added to the cooled (0°C) mixture. After 30 min. at room temperature, hydrolysis and work-up as usual, a 70% yield of o-tolualdehyde was obtained.

Generalization of this short and selective synthetic procedure and applications to the obtention of several products of natural origin or of therapeutic interest are presently under investigation.

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