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SONOCHEMICAL BARBIER REACTION WITH ISOCYANATES AND THE SYNTHETIC USE OF THE ORGANOMETALLIC INTERMEDIATE

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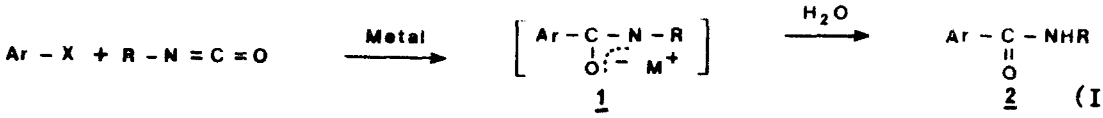
Summary ; Sonication of aryl halides, t-butyl isocyanate and sodium in THF leads to an organosodium intermediate which is easily and regioselectively ortho-lithiated and reacted with electrophilic reagents.

Organometallic addition to isocyanates has been studied in a limited number of papers[1], but it seems that the analogous Barbier procedure has not yet been described[2]. In the continuation of our work in organometallic sonochemistry[3], we found that Reaction (I) can be easily effected from aromatic halides under ultrasonic irradiation.



(I)

The reaction of Bromobenzene and t-Butyl isocyanate in the presence of several metals was chosen as a model. ϕ Br (1 equiv.) and t-BuNCO (1.2 equiv.) were sonicated in diethyl-ether or tetrahydrofuran in a laboratory cleaning bath in the presence of 2 equiv. of the metal until it has disappeared (15-45 min.). Hydrolysis and work-up gave the normally expected amide. Comparative experiments revealed that using lithium results in unusually low yields, in opposition to the favourable behaviour of this metal in many Barbier syntheses[4]. Contrastingly, magnesium gave the secondary amide almost quantitatively (table 1). Chlorobenzene proved to be unreactive under our conditions.

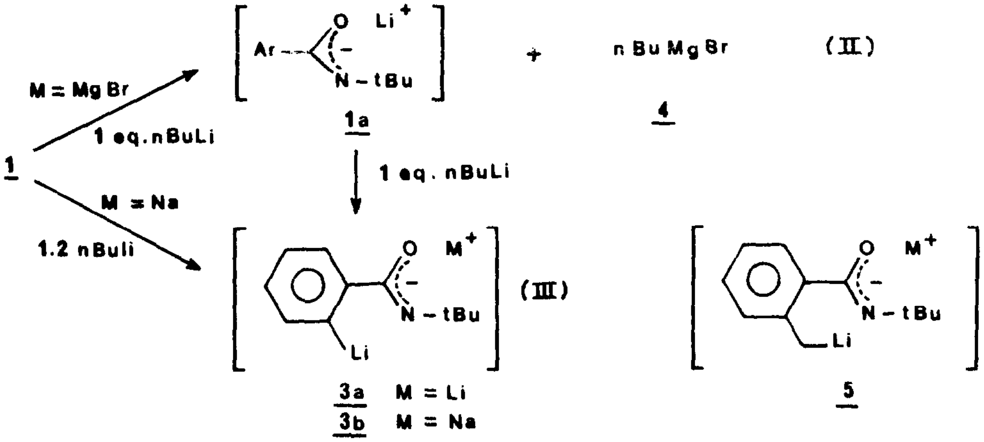
However, the main purpose of this work was not the preparation of simple amides but the use of the reaction intermediate 1 for the further build-up of more elaborated structures via an ortho-directed lithiation step[5,6]. With magnesium as the metal in the first step, lithiation of 1 was attempted by treatment with 1 equiv. of n-Butyl-lithium. Addition of electrophiles showed that virtualy no metallation had occured, probably due to the possible metal exchange (equ. (II)). Access to 3a can only be obtained by treatment of 1 (M = MgBr) with 2 equiv. of base.

Table 1

$$\phi Br + tBu-N=C=O \xrightarrow[\text{Sonication}]{\text{Metal}} \xrightarrow{H_3O^+} \phi CONHtBu$$

Metal	Sonication Condition[a]	Yield %[b]
Li powder	Et_2O , 15 min.	51
Mg powder	THF , 15 min.	91
Na piece	THF , 1 equiv. HMPA , 45 min.	78
—	THF , 1 equiv. HMPA , no sonication, 48h stirring	53
K piece	THF, 90 min	75

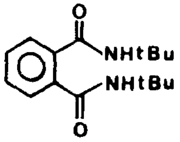
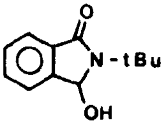
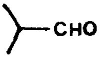
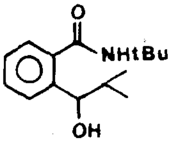
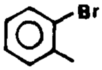
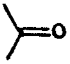
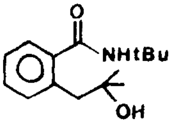
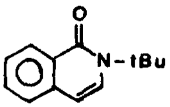
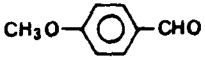
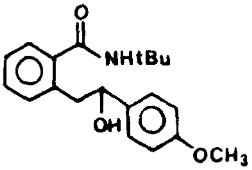
[a] Sonications were run at room temperature. [b] Isolated yield of crystallised product.



Trapping the mixture with an electrophile necessitates its use in large excess and leads to separation problems of the products formed by reaction with 3b and 4. Valorisation of our procedure implicated the necessity to suppress the undesired path (II).

Table 2

$$\text{Ar-Br} + \text{tBuNCO} \xrightarrow[\text{U.S.}]{\text{2 Na}} \left[\ \underline{1}\ \ \text{R} = \text{tBu}, \text{M} = \text{Na}\ \right] \xrightarrow[\text{2/ Electrophile}]{\text{1/ nBuLi}} \text{Adduct}$$

Ar - Br	Reaction Conditions	Lithiation Conditions	Electrophile (equiv.)	Adduct (yield)[a]
C_6H_5-Br	U.S. RT 45 min	1.2 nBuLi -78°C to - 20°C in 30 min	(1.2) tBuNCO	 (75 %)
		1.2 nBuLi - 40°C, 60 min	(2) $HCONMe_2$	 (67 %)
		1.2 nBuLi - 40°C, 60 min	(1.2) 	 (63 %)
	U.S. RT 30 min	1.2 nBuLi - 78°C, 60 min	(3) 	 (46 %)
		1.2 nBuLi - 78°C, 60 min	(3) $HCONMe_2$	 (40 %)
		1.2 nBuLi - 78°C, 60 min	(1.2) 	 (63 %)

[a] Isolated crystalline compounds - analytical and spectral data are in agreement with the structures indicated -

The sonochemical reaction (I) occurs slowly with metallic sodium but is greatly accelerated by a stoichiometric amount of HMPA (table 1).Hydrolysis and isolation lead to a satisfactory 78 % yield of amide. Replacing sonication by stirring slows down considerably the process and the yield is only 53 % after 48 h. In the same manner starting from o-Bromotoluene under sonication, compound 2 (Ar = o-tolyl) was obtained in 74 % yield.

The major advantage of this modification appears in the subsequent lithiation step which occurs very readily in the presence of only 1.2 equiv. of n-BuLi. Although no mechanism has yet be evidenced, it is conceivable that, in analogy with Schlosser's bases[7], a complex base is made up from the alkyl lithium and the sodium "enolate", explaining thus the high metallation rate.

Trapping the dimetallated species with carbonyl compounds produces the adducts in satisfactory yields although a systematic optimisation is still under investigation (table 2). From o-Bromotoluene, the corresponding intermediate 1 (M = Na) reacts regioselectively with the lithium base at the benzylic position to give compound 5 which condenses readily with aldehydes and ketones. In some cases, the final product cyclizes spontaneously to yield the benzo fused heterocycle. Till now, the reaction with epoxides gave low yields of no synthetic value. Despite this limitation, the present method reporting the first application to isocyanates of the Barbier reaction in the unusual presence of sodium as the metal, gives an easy access to a variety of structures among which natural and pharmaceutically (analgesics) valuable products[5,8]. Applications to more complicated structures are presently under investigation.

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