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Reaction of *ortho*-Lithiated *N*-Methylbenzamide with 1,2-Diketones: A Novel Highly Efficient Route to *N*-Methylisoquinolin-1-ones

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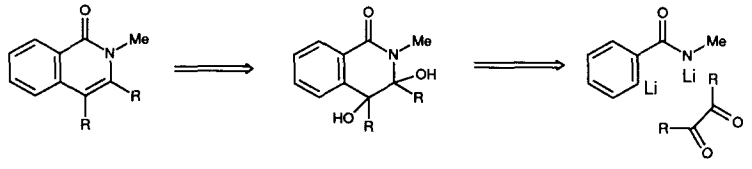
Abstract: 1,2-Diketones were found to react with *ortho*-lithiated *N*-methylbenzamide to give diols **4a-g** in 59-80% yields. Reaction of diols **4a-g** with the system Me_3SiCl/NaI in MeCN furnished *N*-methylisoquinolin-1-ones in 84-92% yields.

The isoquinoline ring is an integral part of many naturally occuring substances.[1,2,3] The importance of isoquinoline derivatives, many of which are pharmacologically active, as intermediates in synthesis of natural products and medicinal chemistry is well documented.[4,5,6] The classical methods of isoquinoline synthesis are the Bischler-Napieralski reaction,[7] the Pictet-Spengler reaction,[8] and the Pomeranz-Fritsch reaction.[9] Numerous modifications of these classical methods have been developed.[10,11,12,13] Systematic division of the synthesis of isoquinolines and their derivatives based on the mode of formation of the pyridine and nonpyridine rings has been introduced.[13]

Direct *ortho*-functionalization of aromatic substrates has been a successful tool for the synthesis of heterocyclic compounds.[14,15,16,17] Application of *N*-methylamide function as a directed metallation group[18] in the remarkable syntheses of 1-aminoquinazolin-2,4-dione and isatins were described recently.[19] Retrosynthetic analysis allowed the author to conclude that *ortho*-lithiated *N*-methylbenzamide may serve as a convenient precursor for the construction of isoquinoline ring (Scheme 1). Reactions of dilithiated *N*-methylbenzamide with carbonyl compounds leading to *ortho*-functionalization of benzene ring are well known.[20,21] However, no data in the literature on similar reactions of *ortho*-lithiated *N*-methylbenzamides with 1,2-dicarbonyl compounds exist.

Scheme 1.



This work is a report of a new and highly efficient method of isoquinolones synthesis based on the reaction of *ortho*-lithiated deprotonated *N*-methylbenzamide with 1,2-diketones followed by convenient aromatization of the resulting diols to isoquinolones. The results of these studies are summarized in Scheme 2.

In a typical experimental procedure[19] *n*-BuLi (2.5 M in hexanes, 8 mL, 20mM)[22] was slowly added to a vigorously stirred solution of *N*-methylbenzamide (1.35g, 10 mM) in 15 mL of dry THF at -78°C under argon. The resulting pale yellow suspension was gradually warmed up to -5°C (water/acetone bath) and stirred at this temperature for an additional 45 min to assure the dimetallation, cooled to -78°C, and solution (or suspension for **3e-g**) of 10 mM of 1,2-dicarbonyl compound in 10 mL of dry THF was added by syringe. The resulting yellow mixture was stirred at this temperature for additional 15 min, slowly warmed up to room temperature (30 min), stirred at room temperature for additional 12-16 hrs, diluted with 50 mL of ethylacetate, aqueous 1.0 N HCl (20 mL) was added, organic layer was separated, washed with 2X30 mL of water, dried over Na_2SO_4, and concentrated. The resulting oil was redissolved in warm ethylacetate (10 mL) and triturated with ether to give precipitate of analytically pure diols **4a-g** (50-65 % yield).[23] Additional 10-15% of diols can be isolated from filtrate by plate chromatography (Silicagel), eluent-hexanes/ethylacetate, 1:3. The procedure was easily scaled up to 0.1 M amounts of substrates. Column chromatography (Fluorosil, 100-220 mesh) and hexanes/ethylacetate, 1:1 eluent were applied for purification in this case.

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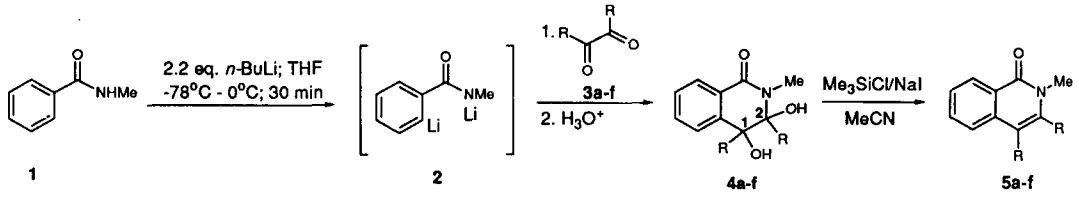
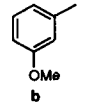
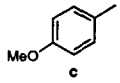
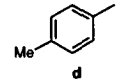
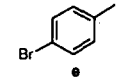
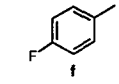
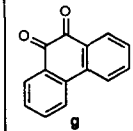
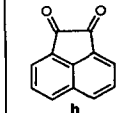
Scheme 2. Reaction of *ortho*-Lithiated *N*-Methylbenzamide with 1,2-Dicarbonyl Compounds as a Key Step in the Synthesis of *N*-Methylisoquinolin-1-ones.



1 **2** **4a-f** **5a-f**

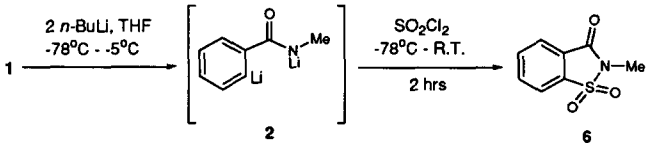
Run	1,2-Diketone, **3** R	Yield[a] of **4**, %	M.p., °C	Elemental Analysis for **4**, Calcd/Found C; H	Yield[a,b] of **5**, %	Elemental Analysis for **5**, Calcd/Found C; H	M.p., °C; found (lit.)[Ref]
1	 **a**	75	209-210	76.50/76.21; 5.55/5.63	92	–	245-246 (245)[24]
2	 **b**	71	200-201	71.09/70.97; 5.72/5.81	84	77.60/77.52; 5.70/5.78	176-177
3	 **c**	80	210-212	71.09/70.85; 5.72/5.88	85	77.60/77.47; 5.70/5.87	161-162
4	 **d**	76	224-226	77.19/77.02; 6.21/ 6.33	87	84.92/84.70; 6.24/6.36	173-174
5	 **e**	74	231-233	52.51/52.38; 3.41/3.53	85	56.32/56.25; 3.22/3.31	194-195
6	 **f**	76	215-216	69.28/69.17; 4.49/4.56	91	76.07/76.01; 4.35/4.41	184-185
7	 **g**	59	256 (dec.)	76.96/76.81; 4.99/4.98	88	85.41/85.32; 4.89/5.03	183-184
8	 **h**	64	197 (dec.)	73.60/73.60; 4.94/4.90[c]	91	84.78/84.61; 4.62/4.75	216-218

[a]All the yields correspond to isolated analytically pure compounds. [b]Reaction time for the conversion of diols **4a-g** into *N*-methylisoquinolin-1-ones **5a-g** was 30-40 min. [c]Analysis corresponds to structure **4f** †/2 H_2O.

All the diols were characterized by ^{1}H, ^{13}C NMR, mass-, and IR-spectroscopy, and elemental analysis. Additional proof for the structures was achieved by extensive decoupling and NOE experiments. ^{13}C NMR spectra of diols **4a-g** ($CDCl_3$; 75 MHz) showed signals at 29.0 ±1.0 ppm (*N*-Me); 78.5 ± 1.0 ppm (C-2); 93.0 ± 2.0 ppm (C-1); 162.0± 2.0 ppm (C=O). Typical mass specrum (EI) of diols showed molecular peak (abundance-12-16%).[23] IR spectra of diols (KBr) showed bands at 3595 (broad, OH stretching vibrations), 1685 (C=O stretching vibrations of amide), and 1045 (C-O stretching vibrations) cm^{-1}.

The resulting diols **4a-g** were converted into *N*-methylisoquinolin-1-ones **5a-g** by the reaction of **4a-g** with the system Me_3SiCl/ NaI in dry MeCN (Scheme 2).[25] In a typical procedure suspension of 1mM of diols **4a-g** and 315 mg (2.1 mM) of dry NaI in 5 mL of dry MeCN was stirred at room temperature for 10 min under argon and 217 mg (2 mM) of freshly distilled Me_3SiCl was added by syringe, after which the reaction mixture immediately turned dark red. After all starting diol **4** was consumed (TLC, hexanes/ ethylacetate, 1:1, reaction times-approximately 30-40 min) the reaction mixture was concentrated, treated with 10% aq $NaHSO_3$, extracted with 3X20 mL of Et_2O, dried over Na_2SO_4, concentrated and purified by plate chromatography (Silicagel, eluent-hexanes/ether, 1:3) to give analytically pure sample of *N*-methylisoquinolin-1-ones (**5a-g**) (Scheme 2). All spectroscopical data as well as elemental analysis of compounds **5a-g** were in agreement with the assigned structures.

Further proof for the importance of the *ortho*-lithiated *N*-methylbenzamide (**2**) as a convenient building block for the heterocyclization was reaction of **2** with sulfuryl chloride leading to formation of sulfonimide **7** in 64% yield.[26]



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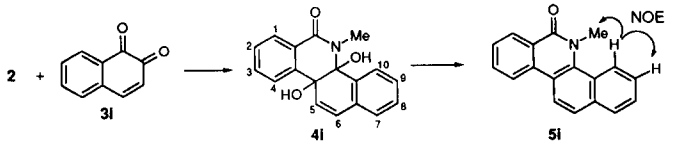
22. Neither application of *tert*-BuLi for dimetallation of *N*-methylbenzamide nor addition of tetramethylenediamine affected the yields of diols **4a-g**.

23. Attempted reaction of **2** with nonsymmetrical 1,2-diketone, 1,2-naphthoquinone (**3l**) furnished single isomer **4l** in 39% yield (starting material **3l** was also isolated from the reaction mixture in 22% yield). Diol **4l** was isolated from the reaction mixture as grey precipitate, m.p. 164-165°C. ^{1}H NMR (DMSO-d_6, 300 MHz) 2.95 (s, 3H, Me), 7.24 (d, J=7.2 Hz, H-4), 7.42-7.53 (m, 3H, H-2, H-3, H-7), 7.63 (t, J=7.8 Hz, H-8), 7.71-7.80 (m, 3H, H-1, H-5, H-6), 7.84 (t, J =7.8 Hz, H-9), 8.12 (d, J=7.8 Hz, H-10); ^{13}C NMR (DMSO-d_6, 75 MHz) 29.69, 79.34, 95.57, 119.18, 122.61, 125.43, 126.14, 127.57, 127.65, 127.73, 127.89, 128.27, 128.42, 128.68, 130.35, 131.61, 132.87, 161.94. Mass spectrum: m/z 259 (47), 276 (100), 293 (M^+, 12). Anal.Calcd. for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15. Found: C, 73.54; H, 5.24. Subsequent treatment of **4l** with the mixture Me_3SiCl/NaI in MeCN led to formation of **5l** in 72% yield. Extensive decoupling and NOE studies of **5l** as well as comparison of m.p. (148-149°C) with the one given in literature (Ninomiya, I.; Naito, T.; Mori, T. *Tetrahedron Lett.* **1969**, *48*, 3643) allowed the assignment of the structure for **5l**, and consequently, for diol **4l**.



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26. Procedure for the synthesis of *N*-methylsaccharine (**6**) was similar to the one described for the synthesis of diols **4a-g**. Product **6** was isolated from the reaction mixture by plate chromatography (Silicagel, eluent-hexanes/ ether, 6:1) and recrystallized from cyclohexane to give analytically pure sample. All spectral and physical data for the compound were in agreement with those for the authentic sample (Hettler, H. *Adv.Heterocycl.Chem.* **1973**, *15*, 233).

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