A New Modification of the Friedländer Synthesis via *ortho*-Dilithiated *N*-Pivaloylanilines

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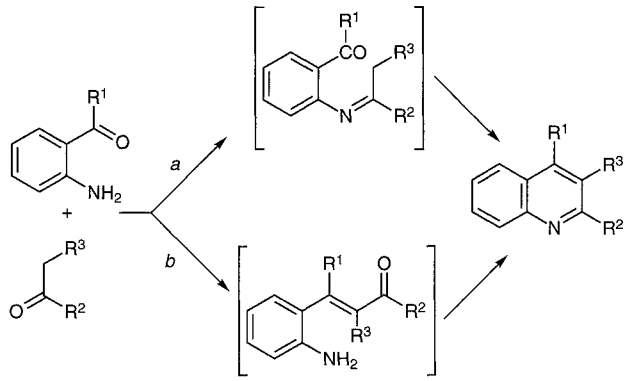
Abstract: Formylation of *ortho*-dilithiated *N*-pivaloylanilines followed by treatment with carbonyl compounds and KHMDS affords 3- or 2,3-substituted quinoline derivatives in a one-pot reaction.

The Friedländer quinoline synthesis has been defined as an acid- or base-catalyzed condensation, followed by a cyclodehydration, between an aromatic *o*-aminoaldehyde, ketone or derivative thereof with an appropriately substituted aldehyde, ketone or other compound containing a reactive α-methylene group.[1-4] More recently, C(α),*O*-dilithiooximes have been also used as reactive α-methylene compounds.[5] Although this synthesis has been known for more than one hundred years, its mechanism is still not completely understood. It is generally accepted that it occurs by the initial formation of a Schiff base followed by cyclization (*a*, Scheme 1), instead of the alternative mechanism (*b*), because of the improbable *E* to *Z* isomerization of the putative unsaturated carbonyl intermediate in the reaction conditions.[4]

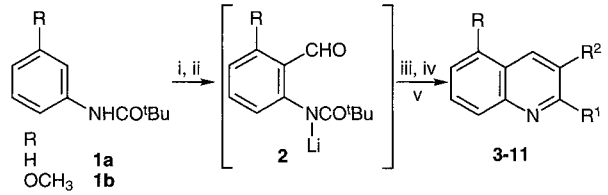


Scheme 1

The main drawback of the Friedländer quinoline synthesis is the relative inacessibility of the *o*-aminobenzaldehydes or ketones required as starting materials, due to their tendency to self-condensation.[6] Alternative procedures so far proposed mostly imply aldol condensations of *o*-nitrobenzaldehydes, followed by reduction and cyclization.[7]

On the other hand, dilithio species derived from *N*-Boc- or *N*-pivaloylanilines are very common reagents in the preparation of quinoline compounds. For instance, in modifications of the Combes synthesis, the reaction of these species with masked malonodialdehyde derivatives (such as vinylamidinium salts or compounds vinylogous of formamide or formic esters) gives, after acidic treatment, the corresponding quinolines.[8] Alternatively *ortho*-formylated compounds derived from pivaloylanilines have been used in Wittig reactions with carbethoxymethylenetriphenylphosphoranes[9] or have been transformed into triphenyl-*o*-aminobenzylphosphoranes,[10] to give finally quinoline derivatives. A general problem, when pivaloylanilines are used as starting materials, is that the removal of the pivaloyl group requires quite vigorous conditions.[11]

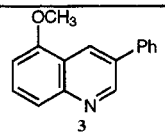
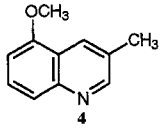
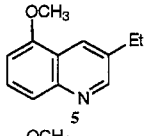
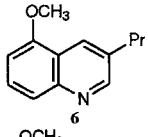
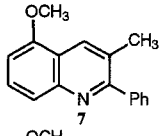
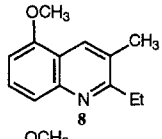
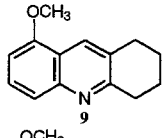
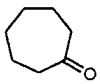
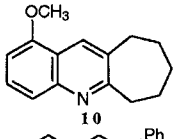
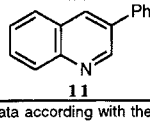
We here report a new modification of the Friedländer quinoline synthesis, also starting from *ortho*-dilithiated species derived from pivaloylanilines,[12] which affords 3- or 2,3-substituted quinoline derivatives in a one-pot procedure without the need for deprotection of the pivaloyl group. In this method, pivaloylanilines **1**, prepared by reaction of the suitable aniline with pivaloyl chloride, were *ortho*-formylated with *sec*butyllithium/dimethylformamide. The formyl derivative **2**, without isolation, was sequentially treated with representative aldehydes or ketones and KHMDS, followed by workup with aqueous ammonium chloride, to give the corresponding quinolines (scheme 2).[13]



i. *sec*-BuLi ii. DMF iii. $R^1COCH_2R^2$ iv. KHMDS v. NH_4Cl

Scheme 2

Table 1. Reactions of *ortho*-lithiated pivaloylanilines (**1**) with carbonyl compounds.*

Entry	Carbonyl compound	Product	Yield %
1	Ph-CH_2-CHO	 **3**	84
2	CH_3-CH_2-CHO	 **4**	46
3	CH_3-(CH_2)2-CHO	 **5**	32
4	CH_3-(CH_2)3-CHO	 **6**	35
5	CH_3-CH_2-CO-Ph	 **7**	85
6	CH_3-CH_2-CO-CH_2-CH_3	 **8**	82
7		 **9**	80
8		 **10**	78
9	Ph-CH_2-CHO	 **11**	81

*All compounds exhibited spectroscopic data according with their structures. Yields refer to pure, isolated compounds.

The yields obtained are summarized in Table 1. Although most of our substrates carried a methoxy substituent, which acts as a cooperating director group in the initial lithiation, this is not an essential requirement, as shown by the comparison of entries 1 and 9. Thus, our method can be considered as general for any pivaloylaniline with a free *ortho*-position.

In conclusion, our method offers a convenient alternative to the Friedländer quinoline synthesis due to the availability and stability of the starting materials, the mildness of the experimental conditions and the good yields generally obtained.

Acknowledgements

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References and Notes

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(12) For other examples of *ortho*-directed lithiation of pivaloyl anilines see for example: a) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133. b) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4758. c) Tamura, Y.; Fujita, M.; Chen, L.-Ch.; Inoue, M.; Kita, Y. *J. Org. Chem.* **1981**, *46*, 3564. d) Reed, J. N.; Rotchford, J.; Stricklan, D. *Tetrahedron Lett.* **1988**, *29*, 5725. e) Hewawasam, P.; Meanwell, N. A. *Tetrahedron Lett.* **1994**, *35*, 7303.

(13) A representative experimental procedure is given below: To a solution of 3-methoxypivaloylaniline (**1b**) (506 mg, 2.48 mmol) in dry THF (10 ml) at 0 °C was added *sec*BuLi (4.75 ml, 6.2 mmol). The solution was stirred for 2 h and freshly distilled DMF (0.29 ml, 3.71 mmol) was added dropwise. The reaction was stirred for one more hour at 0 °C and allowed to warm to room temperature for 12 h. 3-Pentanone (0.05 ml, 2.5 mmol) and a 15% toluene solution of KHMDS (6.6 ml, 4.95 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 10 min and at room temperature for 2h, and then was quenched with a saturated aqueous solution of ammonium chloride (5 ml) and extracted with ether (3x10 ml). The organic extracts were dried over sodium sulphate and the solvent was removed under vacuum. The residue was purified by flash chromatography (silica gel, 1:1 dichloromethane/petroleum ether) leading to 2-ethyl-5-methoxy-3-methylquinoline (**8**) (409 mg, 82% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (t, J = 7.6 Hz, 3H), 2.47 (s, 3H), 2.95 (q, J = 7.6 Hz, 2H), 3.96 (s, 3H), 6.75 (d, J = 7.6 Hz, 1H), 7.48 (dd, J = 8.5 and 7.6 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 8.22 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.0, 19.3, 29.5, 55.6, 103.6, 119.6, 120.8, 128.2, 128.6, 130.6, 147.5, 154.7, 163.5.