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A CONVENIENT SYNTHESIS OF N-ARYLANTHRANILIC ACIDS USING ULTRASONICS IN THE ULLMANN-GOLDBERG CONDENSATION

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Abstract. Ultrasonics efficiently promotes the Ullmann-Goldberg condensation of 2halogenobenzoic acids and primary aromatic amines to obtain various Narylanthranilic acids.

Diphenylamine-2-carboxylic acids and their derivatives such as Narylanthranilic acids are interesting precursors for the synthesis of acridinones,¹ an important class of compounds with a large spectrum of biological effects.

Usually, these compounds are prepared by the Ullmann-Goldberg condensation . In this reaction the substitution of an halogen atom from an ortho-halogenobenzoic acid by a phenylamine is promoted by copper catalysts. The yields of the condensation are usually moderate, rarely excellent and often erratic.² Since many parameters are

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Entry	X (halogen)	Base	Catalyst	Solvent	T (°C)	t (h)	Yield (%)
1	Cl	Potassium	Cu	1-pentanol	110	17-24	20-28
2	Cl	K ₂ CO ₃	Cu	1-pentanol	110-130	7	0
3	Br	K ₂ CO ₃	Cu	1-pentanol	110	15.5	15-38
4	Br	K ₂ CO ₃	Cu/Zn	1-pentanol	110	15-17	22-46
5	Br	K ₂ CO ₃	Cu	1-pentanol	Ultrasonics	1	53
6	Br	K2CO3	Cu/Zn	1-pentanol	Ultrasonics	1.5	55
7	Br	к ₂ со ₃	Cu	M.E.K.	Ultrasonics	2	60
8	Br	K ₂ CO ₃	Cu/Zn	M.E.K.	Ultrasonics	2	69
9	Br	K2CO3	Cu/KI (1/1.5)	M.E.K.	Ultrasonics	2	76

TABLE I. Reaction between o-halogenobenzoic acid and 1

involved in this reaction, the adjustment of the reaction conditions became difficult and results highly depend on basicity or steric hindrance of the aniline partners.³ In this study we are concerned with the coupling of 6-amino-2-chlorobenzothiazole 1, 6amino-1-methylindazole 2, 5-amino-1-methylindazole 3 and ortho-anisidine 4 with ochlorobenzoic acid 5, o-bromobenzoic acid 6 and 2-bromo-3-nitrobenzonic acid 7. An extensive study on the synthesis of N-(2-chloro-benzothiazol-6-yl) anthranilic acid 8 was undertaken and results are summarized on Table I.



The most common method used in our laboratory, described by Claverie and Mattioda,⁴ gives poor yields (entry 1). On the other hand, conditions recommended by Albert¹ were unsuccessful with 5 (entry 2) but give variable yields of condensed product with 6 (entry 3-4). Activation of the catalyst using the copper-zinc couple⁵ slightly improve the yield (entry 4). Since the condensation proceeds under heterogeneous conditions, the use of ultrasonic irradiations have been recently employed with success to improve efficiency of the classical Ullmann reaction (biaryl synthesis)^{6,7,8} and the Ullmann-Goldberg reaction.⁹ Using this technique, the yields are routinely improved (entry 5-6) and the best result was obtained when the reaction was performed in methylethyl ketone as solvent, which is easier to remove, and a trace of potassium iodide (entry 7-9).¹⁰

The use of ultrasonics also allows better yields with other primary aromatic amines 2-4 (table II).

Benzoic acid	Amine	Reaction conditions [*]	Product	Yield (%)
5	2	A	9	41
6	2	В	9	68
5	3	A	10	37
6	3	В	10	48
7	4	A' B'	11 11	68 76

TABLE II. Synthesis of various N-arylanthranilic acids

* A = Potassium o-chlorobenzoate, Cu, 1-pentanol, 110° C, 8h 4

 $B = K_2CO_3$, Cu, 1-pentanol, ultrasonics, 2.5h.

A' = Na₂CO₃, Cu/Zn, EtOH, 85°C, 2h.

B' = Na₂CO₃, Cu/Zn, EtOH, ultrasonics, 2h.

This study have been undertaken to obtain the better set of reaction conditions for the Ullmann-Goldberg condensation. The use of ultrasonic irradiations as well as ethylmethyl ketone as solvent in the Ullmann-Goldberg condensation efficiently improve the yield of the reaction. The N-arylanthranilic acids obtained are valuable intermediates for the synthesis of acridinones and we are currently investigating these reactions.

EXPERIMENTAL

Melting points were obtained with a Mettler FP 61 apparatus and are uncorrected. ¹H NMR spectra were recorded using a VARIAN XL 200 spectrometer with tetramethylsilane as the internal standard. Elemental analyses were performed at the Service de Microanalyse, Faculté de S^t Jérôme, Marseille.

N-(2-chloro-benzothiazol-6-yl) anthranilic acid 8.

A mixture of 6-amino-2-chlorobenzothiazole (1.11g, 6 mmol), ortho-bromobenzoic acid (1.41 g, 7 mmol), anhydrous potassium carbonate (1.11 g, 8 mmol), powdered copper

(0.05 g), potassium iodide (0.01 g), in ethylmethyl ketone (15 ml) was treated for 2 hours with ultrasonic irradiations (Trans-sonic 570/H at 35 kHz). The solvent was removed from the green solution. The residue was treated with 60 ml of hot water, refluxed and then filtered . On acidification to pH = 5-6 with 2N hydrochloric acid, 1.39g (76 %) of N-(2-chloro-benzothiazol-6-yl) anthranilic acid as a greenish solid was obtained by filtration.

m.p. 184-186°C.

¹H NMR (DMSO-d₆) : δ 6.84 (1H), 7.31-7.47 (3H), 7.86-8.00 (3H), 9.80 (1H). Anal. Calcd. for C₁₄H₉ClN₂O₂S: C, 55.2 ; H, 3.0 ; N, 9.2. Found : C, 55.5; H, 3.1; N, 8.9.

N-(1-methyl-indazol-6-yl) anthranilic acid 9.

A mixture of 6-amino-1-methylindazole (2.00 g, 13.6 mmol), ortho-bromobenzoic acid (3.20 g, 15.9 mmol), anhydrous potassium carbonate (2.52 g, 18.2 mmol), powdered copper (0.10 g) in 1-pentanol (40 ml) was treated for 2.5 hours with ultrasonic irradiations. The solvent was removed and the residue was treated with hot 0.1 N sodium hydroxide (60 ml). The dark solution was filtered. On acidification to pH 6 with dilute hydrochloric acid, 2.58 g (68%) of a purplish precipitate was obtained. m.p. 258°C.

¹H NMR (DMSO-d₆) : δ 3.98 (3H), 6.81 (1H), 7.01 (1H), 7.35-7.46 (3H), 7.69 (1H), 7.91-7.95 (2H).

Anal. Calcd. for C16H13N3O2: C, 68.8; H, 4.7; N, 15.1. Found: C, 68.5; H, 4.8; N, 14.8.

N-(1-methyl-indazol-5-yl) anthranilic acid 10.

This compound was obtained as described previously for 9. From 2.00 g (13.6 mmol) of 5amino-1-methylindazole 1.82 g (48 %) of a dark-green precipitate was collected. m.p. 205°C.

¹H NMR (DMSO-d₆) : δ 4.02 (3H), 6.67 (1H), 7.02 (1H), 7.25 (2H), 7.56-7.61 (2H), 7.91-7.94 (2H).

Anal. Calcd. for C16H13N3O2: C, 68.8 ; H, 4.7 ; N, 15.1. Found: C, 69.1 ; H, 5.0 ; N, 15.2.

3-nitro-2'-methoxy-anthranilic acid 11.

A mixture of ortho-anisidine (3.5 ml, 31 mmol), 2-bromo-3-nitro-benzoic acid (5.00 g, 24.9 mmol), anhydrous sodium carbonate (2.50 g, 23.6 mmol), powdered copper/zinc⁵ (0.10 g) in absolute ethanol (25 ml) were treated 2 hours by ultrasonic irradiations. Ethanol was

removed and the residue was treated with hot water and filtered. On acidification to pH 4-5 with 2N hydrochloric acid, an orange precipitate was obtained, which after filtration and washing with water yielded 4.44 g (76 %) of 3-nitro-2'-methoxy-anthranilic acid. m.p. 232° C (litt. 227-228).⁹

¹H NMR (DMSO-d₆) : δ 3.78 (3H), 6.75 (2H), 7.01 (3H), 8.06 (1H), 8.21 (1H), 10.04 (1H).

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