Pergamon

Tetrahedron Letters, Vol. 38, No. 29, pp. 5107-5110, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01138-6

Use of N,N-Dimethylformamide as Solvent in the Synthesis of N-Phenylanthranilic acids.

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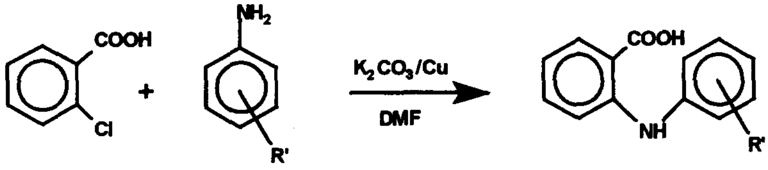
Abstract: It is known that N-phenylanthranilic acids can be synthesized by Ullmann-Goldberg condensation in different conditions. This paper reports some parameters which influence the condensation and reports a general procedure for this reaction using N,N-Dimethylformamide as solvent. © 1997 Published by Elsevier Science Ltd.

N-Phenylanthranilic acid derivatives (I) can be obtained by Ullmann-Goldberg condensation. Recently, we reported a study of some parameters which influence this reaction for the synthesis of I using water as solvent[1]. As a continuation of this work, we studied the synthesis of these compounds with N,N-dimethylformamide (DMF) as solvent.



(I)

RESULTS AND DISCUSSION

The use of DMF as a solvent in the Ullmann Goldberg condensation[2,4] has been reported. The reaction was run under a nitrogen atmosphere[2], in dry DMF (without specifications)[3] with an excess of base [2,4].

The use of one equivalent of K_2CO_3 per mole of *o*-chlorobenzoic acid allows the use of water in this reaction[1]. When DMF is employed as solvent, it is not possible to eliminate water that is formed during the neutralization. This water remains in the reaction media and can affect the copper complex formation when an excess of K_2CO_3 is present .

Table 1 shows yields obtained from different experiments of the condensation between *o*-chlorobenzoic acid and aniline in DMF, with different quantities of K_2CO_3 and copper powder as catalyst (4% in weight relative to *o*-chlorobenzoic acid). In all cases the reaction time was 4 hours.

Table 1. Effect of potassium carbonate on the reaction yield, DMF as solvent.

K_2CO_3 (equiv.)	0.25	0.5	0.75	1	1.5	2	2.5
Yield (%)	34	51	67	82	75	57	37

Experiments were performed to establish the neccesary moles of amine for the reaction. For a molar ratio of *o*-chlorobenzoic acid : aniline 1:1, 1:2, 1:3 the yield was 70, 82 and 84%, respectively. In all cases, 1 equivalent of K_2CO_3 and copper powder as catalyst (4% w/w referred to *o*-chlorobenzoic acid) was used. The product obtained with 3 equivalents of amine was more difficult to purify.

The reaction time was studied using 1 equivalent of K_2CO_3, 2 moles of aniline per mole of acid and copper powder (4% w/w refered to *o*-chlorobenzoic acid). Experimental results demonstrated that reaction time of 2 hours was sufficient.

Table 2. Effect of the reaction time on yield.

Time	20'	40'	1h	2h	4h	6h
Yield (%)	22	66	76	81	82	82

To determine the quantity of copper, several experiments were performed using 2 moles of amine and 1 equivalent of K_2CO_3 in DMF.

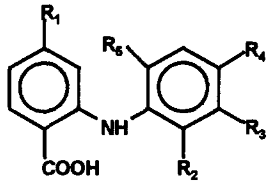
As shown in Table 3 the use of 3% copper powder (w/w related to *o*-chlorobenzoic acid) was sufficient for good yields in two hours reaction time.

Table 3 Effect of copper on the reaction yield.

Cu (%)	1	2	3	4	6
Yied(%)	73	74	79	81	80

Table 4 shows several N-phenylanthranilic acids derivatives obtained using DMF as solvent under the conditions described above.

Table 4. Results of the synthesis of N-phenylanthranilic acids derivatives.



No	R1	R2	R3	R4	R5	Yield* (%)	m.p. °C (uncorr.)	m.p. °C (lit.)	Ref.
1	H	H	CF_3	H	H	60	125	125	5
2	H	H	H	COOH	H	66	289-91	290	6
3	NO_2	COOH	H	H	H	80	326	324-25	7
4	Cl	H	H	NO_2	H	49	234	235	8
5	H	COOH	H	H	H	81	294	294	9
6	H	H	H	Cl	H	82	177	177	10
7	H	H	MeO	H	H	72	132	132	11
8	H	H	CH_3	H	H	63	139	139	12
9	H	CH_3	CH_3	H	H	70	231-2	230-1	13
10	H	Cl	CH_3	H	Cl	18	255	255.5-57.5	2

*Recrystallized

GENERAL PROCEDURE

A mixture of o-chlorobenzoic acid (0.04 mole), substituted aniline (0.08 mole), anhydrous K_2CO_3 (0.02 mole), copper powder (0.2 g) and DMF (25 mL) was kept at reflux for two hours. The mixture is slowly added with shaking to a HCl (1:1) solution (100 mL) then left to stand overnight. The crystallized N-phenylanthranilic acid was filtered and washed with water, extracted with boiling water and crystallized from appropriate solvent.

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(*Received in USA* 19 *March* 1996; *revised* 25 *March* 1997; *accepted* 2 *June* 1997)