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Use of Pyridine as Cocatalyst for the Synthesis of 2-Carboxy Substituted Diphenylethers by Ullmann-Goldberg Condensation

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USE OF PYRIDINE AS COCATALYST FOR THE SYNTHESIS OF 2-CARBOXY SUBSTITUTED DIPHENYLETHERS BY ULLMANN-GOLDBERG CONDENSATION

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Abstract: The synthesis of 2-carboxy-diphenylethers from o-chloro-benzoic acid and phenols is reported using water as solvent and copper, cuprous iodide and pyridine as catalysts.

Diphenylethers are useful as herbicides[1,2], ignifuges[3], antiinflammatories[4,5], and also as intermediates in the synthesis of xanthones[6,7], p-dibenzo-furans[8,9], and p-dibenzo-dioxines[10]. The interest in the synthesis of these compounds goes back to the beginning of the century[11]. This work is a logic continuation of the results reached in our group around the Ullmann-Goldberg condensation reaction[12-15], which showed that water can be employed in this reaction with good results. Here we present the procedure for the synthesis of 2-carboxy-diphenylethers using water as solvent.

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RESULTS AND DISCUSSION

The 2-carboxy substituted diphenylethers (III) can be obtained by the traditional dry Ullmann method or by the condensation of o-halogen-benzoic acid derivatives (I) with substituted phenols (II) in nitrobenzene or iso-amyl alcohol (figure 1).

When the condensation was accomplished with water as solvent, one equivalent of K_2CO_3, and copper powder as catalyst, as reported for the synthesis of N-phenyl-anthranilic acids[15], the corresponding 2-carboxy-diphenylether was not obtained. The same result was obtained when reaction was catalyzed with cuprous iodide alone or mixed with copper powder. Nevertheless, if pyridine and o-clorobenzoic acid were added in a molar ratio of 0.5:1 using copper powder as catalyst, the expected 2-carboxy-diphenylether was obtained although in low yield (only 9%). In all experiments, the reaction time was 6 h and the molar ratio phenol:o-chlorobenzoic acid was 2:1. As the phenol acidity can interfere with the normal course of the condensation, we performed some experiments changing the K_2CO_3 equivalent number. These results are shown in Table 1.

It is noteworthy that when we used more than 4 equivalents of K_2CO_3, the yield of the acid remained constant. It was observed that in employing CuI, the yield of the desired product was increased. Thus, using copper powder together with CuI, Py and 4 equivalents of K_2CO_3, the o-chlorobenzoic acid was condensed in six hours with phenol to yield 52% of the expected 2-carboxy-diphenylether. In all reactions, salicylic acid was obtained as by-product, which was isolated, together with unreacted o-ClBz.

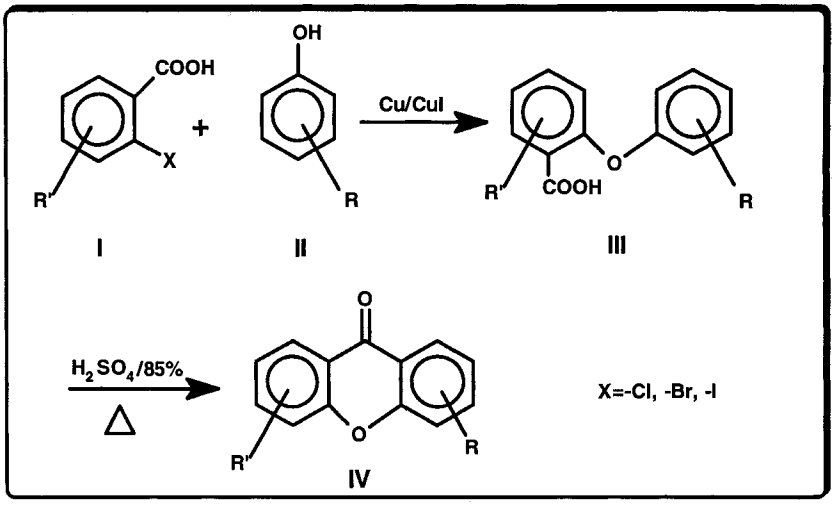


Figure 1

Table 1. Effect of the amount of K_2CO_3 on the yield

Equiv. of K_2CO_3	1	2	2.5	3	4	12
Yield of 2-carboxy-di-phenylether	9	20	15	32	36	37

To establish the minimun of Py necessary for the reaction, some experiments were performed, using the reaction with p-chlorophenol (p-ClPh) as a model. It was found that for a molar ratio of p-ClPhOH:K_2CO_3:o-ClBz:Py 2:2:1:0.5, the yield was the same, and smaller quantities of Py decreased the yield (Tab. 2). In all cases Cu powder was employed together with CuI (3% w/w each refered to o-ClBz). Once the quantity of Py necessary for the condensation was established, the reaction time was reduced with the same yield. All

Table 2. Determination of the optimal reaction time and amount of pyridine needed

Equivalents of pyridine	2	1	0.5	0.25	0.125	0.5	0.5
Time (h)	6	6	6	6	6	4	2
Yield (%)	55	54	56	26	24	56	57

acids were identified by transforming to corresponding xanthones (IV) and compared with original samples.

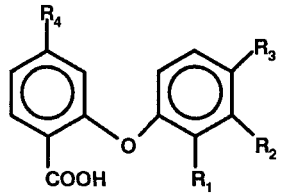
In table 3 are shown the results of the synthesis of substituted 2-carboxy-diphenylethers employing the conditions above. A reaction time less than 2 h decreased the yield.

EXPERIMENTAL PART

1. Synthesis of 2-carboxy-4'-chloro-diphenylether.

A mixture of o-chlorobenzoic acid (6.26 g; 0.04 mol), p-chlorophenol (10.28 g; 0.08 mol), K_2CO_3 anhydrous (11.04 g ; 0.08 mol), pyridine (1.58 g; 0.02 mol), Cu powder (0.2 g) and cuprous iodide (0.2 g) in 25 mL water was kept at reflux for two hours. The mixture was then basified with Na_2CO_3 solution and extracted with Et_2O. The aqueous solution was acidified with HCl, the precipitated solid was filtered off and disolved in NaOH; the basic solution was filtered (charcoal) and acidified with acetic acid. The 2-carboxy-4'-chloro-diphenylether crystalized from the mixture (5.7 g; 57% yield) m.p 114-16 °C (uncorr. lit. 114-16 °C[18]).

Table 3. Results of the synthesis of several 2-carboxy-diphenylethers



№	R_1	R_2	R_3	R_4	Yield (%)	M.P.°C (uncorr.)	M.P.°C (lit.)	Reference
1	H	H	H	H	57	110-12	113	16
2	CH_3	H	H	H	79	134	133.5	16
3	H	CH_3	H	H	63	94-96	95	17
4	H	H	CH_3	H	70	117-19	118.5	16
5	H	H	Cl	H	57	114-16	114-16	18
6	H	H	H	Cl	72	114-16	115	19

Elemental analysis for $C_{13}H_9O_3Cl$

Calculated: C, 62.79; H, 3.65; Cl, 14.26,

Experimental: C, 62.47; H, 3.53; Cl, 14.01

2. Synthesis of 2-chloroxanthone.

A mixture of 2-carboxy-4'-chloro-diphenylether (5.57 g) and sulphuric acid (85%, 50 mL) was heated on water bath at 100°C for one hour and poured into ice (40 g). The solid was filtred off and treated with an excess of diluted NaOH solution, filtered, washed with water and dried, yielding a white solid which was identified as 2-chloroxantone, by comparison with authentic sample (4.24 g; 82% yield) m.p 169-70 °C uncorr. (lit. 169-70°C[20]).

Elemental analysis for $C_{13}H_7O_2Cl$

Calculated:C, 67.70; H, 3.06; Cl 15.37.

Experimental: C, 67.41; H, 2.98; Cl, 15.62.

CONCLUSION

The modification of the Ullmann-Goldberg condensation using water as solvent, must be adapted to the synthesis of 2-carboxy-diphenylethers in order to obtain satisfactory results. It was necessary to include pyridine as cocatalyst to improve yields.

REFERENCES

1.Chui, Y.C., Toxicol.Appl.Pharmacol., 1984, 81, 287.

2.Boeger, P., Agrochemical Regulators, Ovchinnikov, Yu.A. Ed., 1985, pp 47-53

3. Davidson, T.E. & Roberts, C.W., J.Appl.Polym.Sci., 1980 25, 2439.

4. Atkinson, D.C., Godfrey, K.E., Meek, B., Saville, J.F., & Stillings, M.R., J.Med.Chem., 1983, 26, 1353.

5. Atkinson, D.C., Godfrey, K.E., Myers, P.L, Philips, N.C., Stillings, M.R. & Welbourn, A.P., J.Med.Chem., 1983, 26, 1361.

6. Goldberg, A.A., & Wragg, A.H., J.Chem.Soc., 1958, 4227.

7. Goldberg A.A & Walker J., J.Chem.Soc., 1953, 1348.

8. Akermark, B., Eberson, L., Johnson, E. & Pettersson, E., J.Org.Chem., 1975, 40, 1365.

9. Gray, A.P., Dipinto, V.M. & Solomon, I.J., J.Org.Chem., 1976, 41, 2248

10. Gray, A.P., Cepa, S.P., Solomon, I.J. & Aniline O., J.Org.Chem., 1976, 41, 2435.

11. Ullmann, F. and Kipper, H., Ber., 1905, 32, 2120

12. Pellón, R.F. & Rodés, L., Patent Cuba #20744 C07C 85/04, 87/54, 101/04, Nov 28/73;

13. Pellón, R.F. & Rodés, L., Patent Cuba #20962 C07C 63/33, Nov 25/979.

14. Carrasco R., Pellón R., Elguero J., Goya P., & Páez, J.A., Synth. 1989, 19, (11-12), 2077-2080

15. Pellón R.F., Carrasco R. & Rodés L., Synth. Commun., 1993, 23, 10, 1447-1453.

16. Ullmann F. & Zlokasoff M., Ber. 1905, 38, 2111.

17. Goldberg A. & Wragg H. J. Chem Soc. 1958, 4227.

18. Ullmann F. & Wagner C., Ann. 1910, 371, 388

19. Ullmann F. & Wagner C. Ann. 1907, 355, 359.

20. Goldberg I. Ann., 1909, 370, 142.

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