

Dedicated to Professor Dr. ALEXANDRU T. BALABAN, member of the Roumanian Academy on the occasion of his 75th anniversary

A NEW DIRECT SYNTHESIS OF AROMATIC AMIDES IN THE PRESENCE OF TRIETHYL PHOSPHITE AND 4-DIMETHYLAMINOPYRIDINE

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Aromatic amides have been prepared in high to moderate yields by a new direct synthesis from aromatic carboxylic acids and aromatic amines in the presence of a novel reagent, namely triethyl phosphite-4-dimethylaminopyridine (TEP-4-DMAP), using pyridine as a solvent, at 120-130°C for 6-8 hours.

INTRODUCTION

Since the 1960s, research has been focused on finding new, simpler, rapid, more effective and quantitative methods in order to offer an alternative to the classic ways for condensates synthesis. One of the most used is the direct condensation reaction. We synthesized and reported on various compounds obtained by this method. These syntheses were performed in the presence of novel activating agents containing a heteroatom, such as boron and phosphorus, which we identified, tested, and successfully promoted.¹⁻⁸

As is well known, a common method to prepare N-monosubstituted amides uses the reaction of primary amines with acyl chlorides or anhydrides of carboxylic acids. The latter compounds are often prepared by the reaction of a carboxylic acid with reagents which are very aggressive towards the human body and the environment. The conversion of the two-steps process into a one-step procedure was successfully promoted by scientists.^{9,10}

Concerning the aromatic amides obtained by direct condensation, several pathways are known, each one involving various reagents. Among them, reactive phosphorous compounds are known for their efficiency. We already reported on some of them, such as triacylphosphites,¹¹ diacylphenylphosphites,¹² triacylphosphates,¹³ ethylenechlorophosphite,¹⁴ phosphorous acid-iodine,^{15,16} and phenyldichlorophosphite.¹⁷

Despite of the wide series of triaryl phosphites used for the synthesis of aromatic amides and aromatic polyamides, triphenyl phosphite being the most known for its applications,^{18,19} trialkyl phosphites under similar conditions were never reported as reagents in this field.

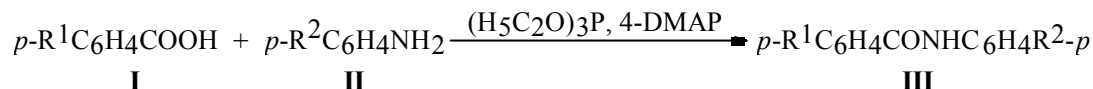
Consequently, we aim at identifying new activating systems in order to obtain aromatic amides by direct condensation and to test them on low molecular weight products. Based on the experimental data, we intend to apply these activating systems on aromatic polyamides.

By stepwise investigation, we are now able to prove that direct synthesis of aromatic amides is possible in the presence of a novel activating system TEP-4-DMAP, based on triethyl phosphite and 4-dimethylaminopyridine, as a base. TEP-4-DMAP was not reported in the literature until now as a reagent for direct synthesis of aromatic amides.

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RESULTS AND DISCUSSION

By stepwise investigation, we established that aromatic carboxylic acids **I** do react with aromatic amines **II** in the presence of TEP and 4-DMAP, in the mole ratios of 1:1.5:1:1, to yield aromatic amides **III**, as presented in Scheme 1.



III	a	b	c	d	e	f	g	h
R ¹	CH ₃	CH ₃	CH ₃	H	H	H	Cl	Cl
R ²	CH ₃	H	NO ₂	Cl	CH ₃	H	CH ₃	Cl

Scheme 1 – Direct synthesis of aromatic amides in the presence of TEP-4-DMAP.

The most important factors which influence the efficiency of this novel activating agent were studied, as follows: the amount of aromatic amine **II** and of TEP-4-DMAP, the solvent, the reaction temperature, the structure of acids and amines employed, the reaction time.

Using 1.5 mole of aromatic amine **II** for 1 mole of aromatic carboxylic acid **I**, good yields were obtained. When stoichiometric amounts were employed (no excess of amine **II**), the yields decreased.

For 1 mole aromatic carboxylic acid **I**, 1 mole triethyl phosphite (TEP) was required, although TEP contains three identical functional groups, but with gradually decreasing reactivity, characteristic for many phosphorus compounds. The yields also decreased when the amount of triethyl phosphite decreased. Some tertiary amines, other than 4-DMAP, were tested as bases (such as trialkyl amines, pyridine, N-methylimidazole, etc.), but the most efficient resulted to be 4-DMAP. In its absence, the reaction underwent no significant conversion and was difficult to perform. The optimum amount of 4-DMAP was 1 mole for 1 mole of aromatic carboxylic acid **I**.

In many reactions, pyridine is used as base, but in this synthesis we used pyridine as a solvent, because the yield was too modest with pyridine as base and in the absence of 4-DMAP.

This synthesis required moderate temperatures of about 120-130°C, during 6-8 h, as presented in Table 1.

Table 1

Aromatic amides obtained in the presence of TEP-4-DMAP

Aromatic amides ^a	Yield ^b (%)	Reaction time (h)	M.p. ^c (°C)	Literature m.p. (°C)
IIIa	86	6	160-161	160-162 ²⁰
IIIb	82	7	144-145	144-145 ²¹
IIIc	57	8	200-202	201-202 ²²
III d	61	8	192-194	193-194 ²³
III e	79	7	156-157	157-158 ²⁰
III f	74	7	160-162	161-162 ²⁴
III g	76	7	214-216	215-216 ²⁵
III h	72	8	207-208	207-208 ²³

^a The aromatic amides were identified by comparison of their m.p. and IR spectra with authentic samples.

^b Yields calculated based on the aromatic carboxylic acids **I** employed.

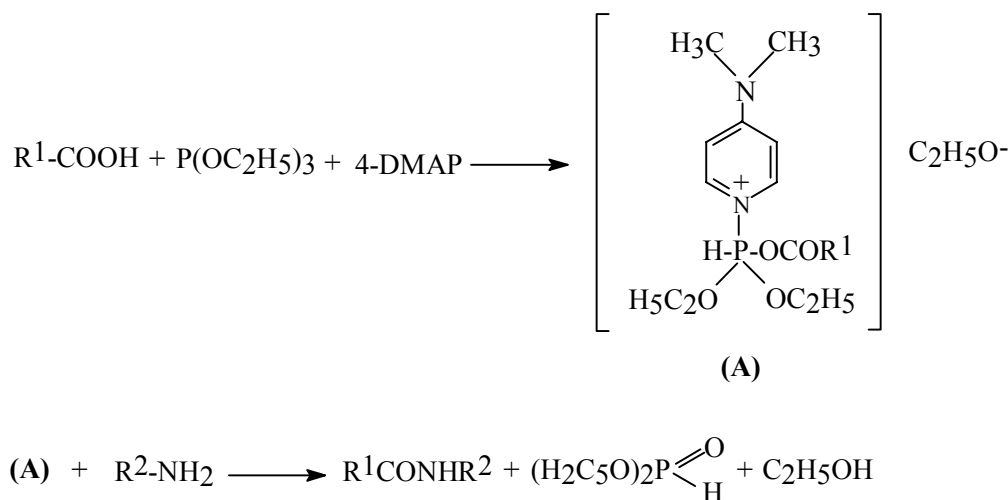
^c After recrystallization.

At lower temperatures, the yields decreased. For example, the yield for product **IIIa** decreased to 30-35% when the reaction was performed at 60-70°C for 7 h.

As can be seen in Table 1, we obtained amides **III** in yields ranging from 57% to 86%. The structures of the aromatic carboxylic acids **I** and the aromatic amines **II** also influenced the yields of this reaction by determining the reaction conditions. Aromatic amines **II** with electron-donating groups lead to increased yields (*i.e.*, amine **IIa** which bears a $-\text{CH}_3$ substituent led to corresponding aromatic amide in a yield of 86%, compared to amine **IIc** which has a $-\text{NO}_2$ group and resulted in the corresponding amide in a yield of 57%).

The mechanism of this reaction is a difficult problem, because the formation of ethyl *p*-toluate as a reaction intermediate is excluded, as demonstrated previously.^{26,27}

Under these circumstances, we propose a mechanism occurring through an acyloxy N-phosphonium salt of 4-DMAP (**A**), formed by a de-ethylation during the reaction of TEP-4-DMAP with the carboxylic acid, according to Scheme 2.



Scheme 2 – Mechanism of direct synthesis of aromatic amides in the presence of TEP-4-DMAP.

A similar mechanism has been proposed by Yamazaki for the synthesis of aromatic polyamides with triphenyl phosphite (TPP) and pyridine,^{28,29} although triphenyl phosphite is able to undergo a mechanism by an ester intermediate. The detailed mechanism of our reaction will be discussed in a separate communication.

EXPERIMENTAL

Materials

In order to obtain results with high accuracy, we chose pure reagents (Fluka, Merck, Aldrich). The solvents were purified and dried before use by specific methods.

Measurements

Melting points were determined with a Gallenkamp hot-block point apparatus.

Infrared spectra were registered on KBr pellets using a Specord M80 Carl Zeiss Jena spectrophotometer.

General procedure for the synthesis of aromatic amides

In a 100 mL three-necked Claisen flask equipped with a thermometer, 0.01 mole of acid, 0.015 mole of amine, 1.3 g (0.01 mole) of 4-DMAP, 1.7 mL (0.01 mole) of triethyl phosphite and 2 mL of pyridine were added. An air-cooled reflux condenser which was extended with a water-cooled reflux condenser was attached. The flask was heated at 120-130°C for 6-8 hours. At the end of the reaction, the final solution at 30-35°C was stirred with 70-80 mL of icy water and then with a NaOH solution (20%) up to pH=9-10, when the aromatic amide precipitated. The product was filtered, washed with 15-20 mL of cold water, 15-20 mL of cold HCl solution 5% and, finally, with 15-20 mL of cold water, and then dried. Yields ranged from 57% to 86%. Structural confirmation for all products was obtained by melting point determinations and IR spectrometry.

CONCLUSION

This paper presents a series of aromatic amides obtained in high to moderate yields from the corresponding carboxylic acids and amines by direct condensation, in the presence of a novel, simple and efficient reagent, namely TEP-4-DMAP.

This new reagent is the only aliphatic phosphite used as a condensing agent reported up to know in the literature and it is active in this type of direct condensation due to its particular electronic structure and reactivity.

By this method, the classic two-step syntheses, which are difficult to perform and operate with high toxic reagents, are avoided.

The key element of the synthesis mechanism is the reactive intermediate **A** formed by the reaction of aromatic carboxylic acid **I** with TEP-4-DMAP. In the absence of TEP-4-DMAP, under the above specified conditions, this synthesis does not take place.

We intend to perform further experiments in order to establish the TEP-4-DMAP effectiveness for the synthesis of other aromatic condensates.

Considering the data presented in this paper, we are going to transfer our results to a macromolecular scale, especially for obtaining aromatic polyamides in the presence of TEP-4-DMAP as an activating agent.

REFERENCES

1. C. I. Chiriac, F. Tanasă and M. Onciu, *Tetrahedron Lett.*, **2003**, *44*, 3579.
2. C. I. Chiriac and F. Tanasă, *Designed Monomers Polymers*, **2003**, *6*, 277.
3. C. I. Chiriac, M. Sava, M. Țibîrnă, R. Ropot, M. Onciu, V. Lupu and I. Truşcan, *Rev. Roum. Chim.*, **1995**, *40*, 1197.
4. R. Ropot, I. Truşcan and C. I. Chiriac, *Rev. Roum. Chim.*, **1998**, *43*, 153.
5. C. I. Chiriac, M. Onciu, M. Țibîrnă, F. Tanasă, I. Truşcan and R. Ropot, *Rev. Roum. Chim.*, **1998**, *43*, 1065.
6. C. I. Chiriac, M. Onciu, I. Truşcan, F. Tanasă and C. Bădărău, *Rev. Roum. Chim.*, **1999**, *44*, 143.
7. C. I. Chiriac, M. Onciu, F. Tanasă, C. Bădărău and I. Truşcan, *Rev. Roum. Chim.*, **1998**, *43*, 971.
8. C. I. Chiriac, M. Onciu and F. Tanasă, *Molecules*, **2005**, *10*, 481.
9. T. Wieland and B. Heinke, *Chem. Ber.*, **1958**, *91*, 483.
10. G. W. Anderson and R. W. Young, *J. Am. Chem. Soc.*, **1952**, *74*, 5304.
11. C. I. Chiriac, *Rev. Roum. Chim.*, **1979**, *24*, 609.
12. C. I. Chiriac, *Rev. Roum. Chim.*, **1981**, *26*, 1001.
13. C. I. Chiriac, *Rev. Roum. Chim.*, **1982**, *27*, 747.
14. C. I. Chiriac, *Rev. Roum. Chim.*, **1983**, *28*, 863.
15. C. I. Chiriac, *Rev. Roum. Chim.*, **1985**, *30*, 799.
16. C. I. Chiriac, *Rev. Roum. Chim.*, **1993**, *38*, 1327.
17. C. I. Chiriac, M. Onciu, M. Țibîrnă, F. Tanasă and I. Truşcan, *Rev. Roum. Chim.*, **1998**, *43*, 31.
18. N. Yamazaki and F. Higashi, *J. Polym. Sci., Polym. Chem. Ed.*, **1975**, *13*, 1373.
19. E. Marechal, *Bull. Soc. Chim. France*, **1987**, 713.
20. R. F. Heck, *J. Org. Chem.*, **1974**, *39*, 3328.
21. T. H. Chan, *J. Org. Chem.*, **1969**, *34*, 2767.
22. H. R. Snyder, *J. Am. Chem. Soc.*, **1954**, *76*, 3039.
23. P. A. Petyunin, *Z. Obsh. Khim.*, **1958**, *28*, 739.
24. K. Inomata, *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 1866.
25. P. Grammaticakis, *Bull. Soc. Chim. France*, **1963**, 871.
26. S. M. Aharoni, W. B. Hammond and J. S. Szobota, *J. Polym. Sci., Polym. Chem. Ed.*, **1984**, *22*, 2567.
27. S. M. Aharoni, W. B. Hammond and J. S. Szobota, *J. Polym. Sci., Polym. Chem. Ed.*, **1984**, *22*, 2579.
28. N. Yamazaki, *Tetrahedron*, **1974**, *30*, 1323.
29. N. Yamazaki, *Tetrahedron Lett.*, **1972**, *28*, 5047.