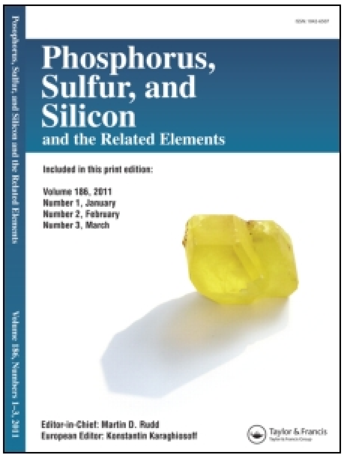


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Phosporylation of Aniline Derivatives in Biphase Systems

Gheorghe Ilia[a]; Mihaela Petric[a]; Lavinia Macarie[a]; Smaranda Iliescu[a]; Adriana Popa[a]
[a] Institute of Chemistry, Timisoara, Romania

To cite this Article Ilia, Gheorghe , Petric, Mihaela , Macarie, Lavinia , Iliescu, Smaranda and Popa, Adriana(2006) 'The Phosporylation of Aniline Derivatives in Biphase Systems', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 7, 1717 — 1723

To link to this Article: DOI: 10.1080/10426500500536614

URL: http://dx.doi.org/10.1080/10426500500536614

Phosphorus, Sulfur, and Silicon, 181:1717–1723, 2006
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500536614

The Phosporylation of Aniline Derivatives in Biphase Systems

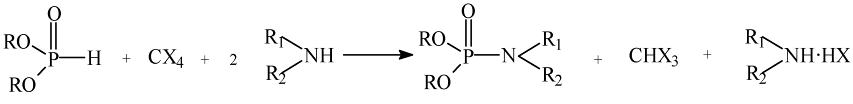
Gheorghe Ilia
Mihaela Petric
Lavinia Macarie
Smaranda Iliescu
Adriana Popa
Institute of Chemistry, Timisoara, Romania

Aniline derivatives were phosphorylated in biphase systems using three methods. A comparative study was performed. The best results were obtained when a solid–liquid system was used. This method is the easiest and lead to higher yields (54–81%).

Keywords Aniline derivatives; liquid–liquid; phosporylation; solid–liquid

INTRODUCTION

Phosphoramidic acid derivatives gained importance because of their use as biological compounds and intermediates in organic synthesis.[1–3] The general procedure developed by Atherton et al.[4] and Todd[5] for the phosphorylation of amines uses as a base an amine and the system phosphite/tetrahalomethane (Reaction 1).



REACTION 1

This method is useful for the phosphorylation of ammonia, but has several drawbacks in the case of amines as the following:

1) From the two moles of amine used, one mole is inevitably lost as the corresponding chlorohydrate.

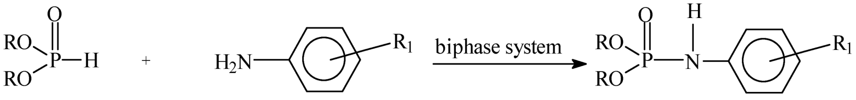
Received February 22, 2005; accepted September 20, 2005.

Address correspondence to Gheorghe Ilia, Institute of Chemistry, 24 M. Viteazul Bv., Timisoara 300223, Romania. E-mail: ilia@acad-icht.tm.edu.ro

2) The separation of the amine salt is laborious and sometimes ineffective.
3) The partial monodebenzylation[6] occurs when dibenzylphosphite is used.

Zwierzak[7] has shown that the phosphorylation of amines can occur in an aqueous system in the presence of a catalytic (about 5% mol) amount of triethylbenzylammonium chloride.

In this article, we present the results obtained in the phosphorylation of aniline derivatives in liquid–liquid systems and liquid–solid systems (Reaction 2).

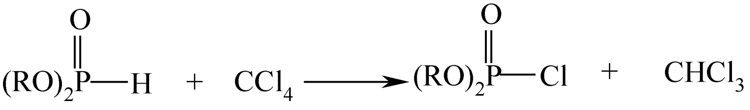


REACTION 2

RESULTS AND DISCUSSION

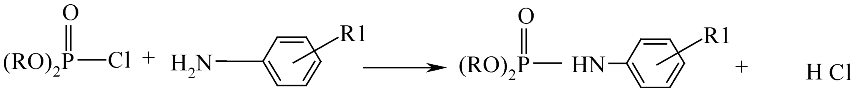
Three methods were used in this study. Methods A and B were performed in a liquid–liquid system, and Method C was performed in a liquid–solid system. The Method C is not mentioned in the literature for the synthesis of such compounds.

Using the system phosphite/tetrachloromethane in the phosphorylation of aniline derivatives, the phosphite is oxidized to chlorophosphate, which reacts with anilines by a nucleophilic substitution, and phosphoramidic derivatives are obtained (Reactions 3 and 4).



$$(RO)_2P(=O)—H + CCl_4 \longrightarrow (RO)_2P(=O)—Cl + CHCl_3$$

REACTION 3



REACTION 4

The hydrochloric acid is neutralized by the base.

The use of standard 50% aqueous sodium hydroxide for the first two methods led to side reactions with a formation of halocarbene followed by its subsequent reaction with anilines[8] (Reaction 5).

$$CHCl_3 + NaOH \rightleftharpoons Cl_3C^{-}\,{}^{+}Na + H_2O \rightleftharpoons NaCl + :CCl_2 + H_2O$$

REACTION 5

Also, when this concentration was used, other side reactions were detected: (a) the hydrolysis of phosphites, especially diphenyl, dibenzyl, and long chain alkyl phosphites; and (b) the formation of dark-brown, tarry contaminants. These possible side reactions could be reduced if the concentration of the aqueous base was below 30% and the temperature was kept below 10°C during the addition of reagents. The use of an excess of a phosphorylating agent was essential because some of the phosphite was lost during the reaction by an anionic dealkylation in an aqueous medium.

Also, the stirring speed and reaction time influenced the yields (Figures 1 and 2).

The best results were obtained at 600rpm and reaction time of 2 h. The influence of a phase transfer catalyst was also studied. The best results were obtained with tetrabutylammonium bromide (Table I).

These studies allowed a few observations:

1) To obtain good yields, the concentration of aqueous sodium hydroxide has to be below 30%.

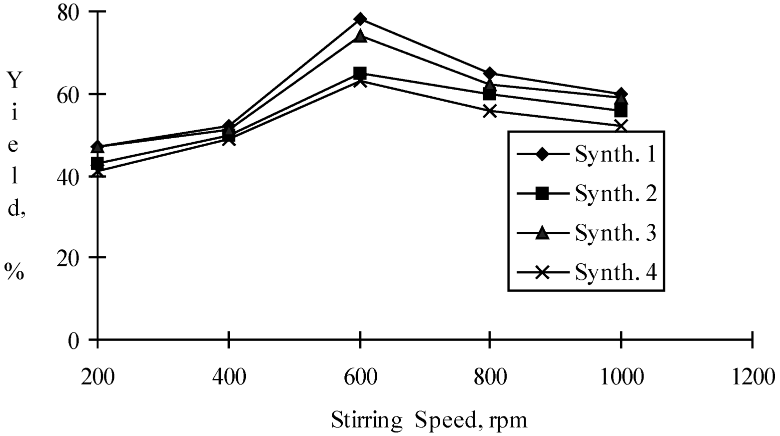


FIGURE 1 The influence of the stirring speed on the yield.

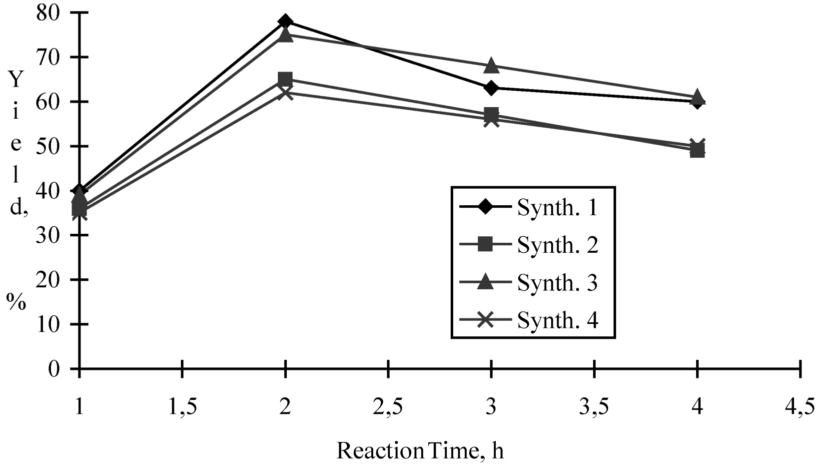


FIGURE 2 The influence of the reaction time on the yield.

2) The use of an excess of dialkylphosphite is necessary due to saponification reactions.
3) The order of reagent addition is important.
4) The solvent is important.

Also, the system of a liquid–solid was used. Solid potassium carbonate was used as a base. In these cases, side reactions were reduced to a minimum because potassium carbonate is a weaker base.

In accordance with the general procedures, reactions were performed with different aniline derivatives and hydrogen phosphites in liquid–liquid and liquid–solid systems. The obtained results are presented in Table II.

TABLE I The Influence of the Catalyst on the Yield

R	R_1	Catalyst	Yields, %
C_2H_5	H	TBAC	71
	p-NO_2	TBAC	57
C_4H_9	H	TBAC	70
	p-NO_2	TBAC	55
C_2H_5	H	TBAB	78
	p-NO_2	TBAB	65
C_4H_9	H	TBAB	75
	p-NO_2	TBAB	62

TBAC(B) = tetrabutylammonium chloride (bromide).

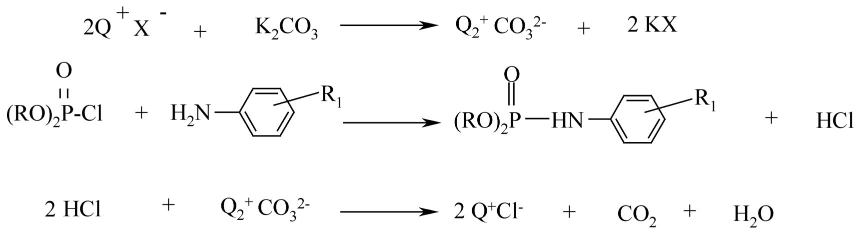
TABLE II Results Obtained in the Phosphorylation of Aniline Derivatives

Synth	R	R_1	Method A Yield, %	Method B Yield, %	Method C Yield, %	^{31}P NMR,[a] δ, ppm
1	C_2H_5	H	78 (77[7])	43 (35[7])	81	2.35
2		*p*-NO_2	65	—	70	0.55
3	C_4H_9	H	75	40	78	3.00
4		*p*-NO_2	62	—	69	1.27
5	*i*-C_4H_9	H	62	38	68	2.57
6		*p*-NO_2	56	—	59	1.10
7	$C_{10}H_{21}$	H	72	39	74	2.78
8		*p*-NO_2	58	—	67	0.72
9	*i*-C_8H_{17}	H	64	37	70	2.90
10		*p*-NO_2	51	—	57	0.83
11	$CH_3(CH_2)_3CH(C_2H_5)CH_2$	H	62	36	71	3.40
12		*p*-NO_2	53	—	56	0.91
13	C_6H_5	H	46	50	67	−17.70
14		*p*-NO_2	38	—	50	−17.74
15	$C_6H_5{-}CH_2$	H	48 (40[7])	41	63	2.55
16		*p*-NO_2	40	—	54	0.67

[a] ^{31}P NMR spectra were performed with Bruker Avance DRX 400 and were measured in a $CDCl_3$ solution using 85% H_3PO_4 as an external standard.

As is shown in the Table II, Method B led to the lowest yields. Phosphoramidates obtained by Methods A and C are formed in good yields. The best results were obtained when potassium carbonate was used as base. In these cases, side reactions were strongly reduced. Even alkyl phosphites with longer chains were used, and the yields were higher. No partial dealkylation was detected for these phosphites.

A mechanism for this method is proposed (Scheme 1).



SCHEME 1

The cation of the catalyst transfers the anion of the base in the organic media, where it reacts with the hydrochloric acid.

The outlined synthetic procedures are particularly convenient for obtaining a wide range of phosphoramidates, especially using Method C, which is the simplest and easy to perform.

EXPERIMENTAL

Method A

A solution of dialkylphosphite (0.011 moles) and the corresponding amine (0.01 moles) in an appropriate solvent (5 mL) (dichloromethane when aniline was used and ethyl acetate when nitroanilines were used) was added dropwise to a stirred two-phase system consisting of dichloromethane (5 mL), tetrachloromethane (5 mL), 25% aqueous sodium hydroxide (5 mL), and a catalyst (0.02 g). The temperature was kept at 0–10°C by external cooling. After the addition was completed, stirring was continued for 1 h at 0–10°C and then for another 2 h at r.t. The organic layer was separated, washed with 3% hydrochloric acid (2× 10 mL) and water (2 × 10 mL), and dried over anhydrous magnesium sulfate, and the solvent evaporated.

Method B

A solution of 25% aqueous sodium hydroxide (5 mL) was added dropwise to a stirred and cooled (0–10°C) mixture of dialkylphosphite (0.011 moles), corresponding amine hydrochloride (0.01 moles), an appropriate solvent (5 mL) (dichloromethane when aniline was used and ethyl acetate when nitoanilines were used), tetrachloromethane (5 mL), and a catalyst (0.02 g). After the addition was completed, stirring was continued for 1 h at 0–10°C and then for another 3 h at r.t. The organic layer was separated, washed with 3% hydrochloric acid (2× 10 mL) and water (2× 10 mL), and dried over anhydrous magnesium sulfate, and the solvent evaporated.

Method C

A solution of dialkylphosphite (0.01 moles) and the corresponding amine (0.01 moles) in an appropriate solvent (5 mL) (dichloromethane when aniline was used and ethyl acetate when nitroanilnes were used) was added dropwise to a stirred two-phase system consisting of dichloromethane (5 mL), tetrachloromethane (5 ml), potassium carbonate (3 g), and a catalyst (0.02 g). The temperature was kept at 0–10°C by external cooling. After the addition was been completed, stirring was continued for 1 h at 0–10°C and then for another 3 h at r.t.

The potassium carbonate and potassium chloride were filtered, and the organic layer was separated, washed with 3% hydrochloric acid (2× 10 mL) and water (2× 10 mL), and dried over anhydrous magnesium sulfate, and the solvent evaporated.

REFERENCES

[1] L. A. Adams, R. J. Cox, J. S. Gibson, M. B. Mayo-Martin, M. Walter, and W. Whittingham, *Chem. Commun.*, 2004 (1998).
[2] C. L. Freel Meyers and R. F. Borch, *J. Med. Chem.*, **43,** 4319 (2000).
[3] I. Tomoskozi, E. Gacs-Baits, and L. Otvos, *Tetrahedron*, **51,** 6797 (1995).
[4] F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 660 (1945).
[5] F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1945).
[6] J. Baddiley, V. M. Clark, J. J. Michalski, and A. R. Todd, *J. Chem. Soc.,* 815 (1949).
[7] A. Zwierzak, *Synthesis,* 507 (1975).
[8] W. P. Weber and G. W. Gokel, *Tetrahedron Lett.,* 1637 (1972).