3-Chloro-3-(dimethoxyphosphoryl)isobenzofuran-1(3*H*)-one – A New Reagent for the Rapid, Convenient Phthaloylation of Amines and Amino Acids in High Yields

Jan Kehler,[1] Eli Breuer*

Department of Pharmaceutical Chemistry, The School of Pharmacy, The Hebrew University of Jerusalem, P. O. Box 12065, Jerusalem, 91120 Israel
Fax +972(2)641-0740; E-mail: breuer@cc.huji.ac.il

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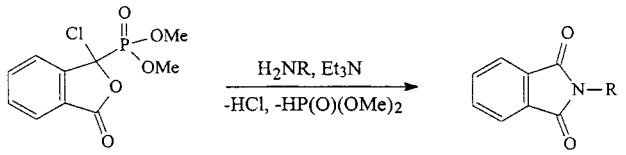
Abstract: 3-Chloro-3-(dimethoxyphosphoryl)isobenzofuran-1(3*H*)-one **(1)** reacts rapidly with aliphatic amines and with amino acids at room temperature to give phthalimides in high yields.

Key words: phthaloylation, protected primary amines, phthalimides, 3-chloro-3-(dimethoxyphosphoryl)isobenzofuran-1(3*H*)-one

In the course of our studies on acylphosphonates and derivatives,[2] we recently examined the chemistry of 3-chloro-3-(dimethoxyphosphoryl)isobenzofuran-1(3*H*)-one **(1)** which was reported by Berlin and co-workers over 30 years ago to be formed in the Arbuzov reaction of phthaloyl dichloride with trimethyl phosphite.[3] In this communication we wish to report that, in the presence of a tertiary amine **1** reacts rapidly with primary amines to give phthalimides **2** in high yields (Scheme 1).



1 **2** 77-91%

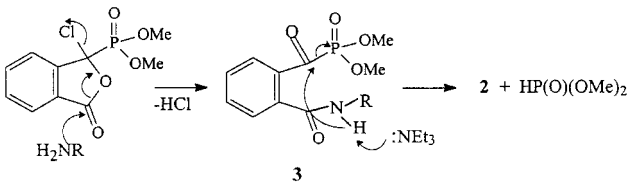
Scheme 1

The phthaloyl group is a well-established protective group for primary amines[4] in various types of compounds, particularly peptides,[5] aminoglycosides,[6] β-lactam antibiotics[7] and in aminoacylphosphonic derivatives.[8]

Several methods exist for the phthaloylation of amines.[9] Prominent among them is the mild method based on *N*-ethoxycarbonylphthalimide.[10] Our method is comparable in mildness and ease with that based on *N*-ethoxycarbonylphthalimide and appears to be superior to a method based on PyBOP published very recently.[11] Compound **1** is easier to prepare than *N*-ethoxycarbonylphthalimide.[10]

The byproduct in our reaction is dimethyl phosphite, the formation of which can be monitored by ^{31}P NMR spectroscopy directly in the reaction mixture (compound **1**: δ_P = 7.9; dimethyl H-phosphonate: δ_P = 9.9, d septet, $^1J_{HP}$ = 710 Hz, $^3J_{HP}$ = 10 Hz), thus making it possible to follow the progress of the reaction. Using this technique it was possible to establish that the reactions are complete in about 10 minutes at room temperature.

The results obtained are listed in the Table. The products obtained were identified by their ^1H NMR spectra. Their melting points were identical with those published in the literature. From the high yields obtained from isopropylamine and *tert*-butylamine it is apparent that the reaction is practically insensitive to the steric effect of the alkyl group. The limitation of the reagent seems to be its lack of reactivity with aromatic amines, as exemplified by aniline. The demethylation of the reagent **1** in this case was probably caused by the nucleophilic action of triethylamine.[12]



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Scheme 2

The mechanism of the reaction can reasonably be assumed to involve attack of the amine on the carbonyl group in **1** leading, by ring opening and the elimination of HCl, to a dimethyl 2-carbamoylbenzoylphosphonate[13] **3**, which further cyclizes to the final product by eliminating dimethyl phosphite (Scheme 2).

Table. Summary of Reactions of **1** with Amines and Amino Acids

Entry	Amine	Yield (%) of **2**	Method	mp (°C) (Solvent)	Lit. mp (°C)	^1H NMR ($CDCl_3$), δ
1	methylamine	89	A	132–134 (MeOH)	134[15]	7.76–7.61 (m, 4H), 3.10 (s, 3H)
2	isopropylamine	91	A	83–85 (MeOH)	85[16]	7.82–7.68 (m, 4H), 4.55 (quint, 1 H), 1.5 (d, 6H)
3	*tert*-butylamine	85	A	45–46 (MeOH)	53[17]	7.78–7.66 (m, 4H), 1.70 (s, 9H)
4	glycine	88	B	191–193	193–195[10]	7.88–7.76 (m, 4H), 5.0 (s, br, 1H), 4.49 (s, 2H)
5	L-phenylalanine	80	B	175–177	178[10]	7.80–7.67 (m, 4H), 7.17 (m, 5H), 5.8 (s, br, 1H), 5.22 (t, 1H), 3.59 (d, 2H)
6	L-glutamic acid	77	B	158–160	160[10]	7.80–7.67 (m, 4H), 4.48 (t, 1H), 3.28 (m, 4H)[a]
7	aniline	0[b]	A	–	–	–

[a] ^1H in DMSO-d_6.
[b] Complete demethylation of **1** was observed by ^{31}P NMR spectroscopy.

3-Chloro-3-(dimethoxyphosphoryl)isobenzofuran-1(3*H*)-one (1): Trimethyl phosphite (8.4 g, 8.0 mL, 0.069 mol) was added dropwise to neat phthaloyl chloride (14 g, 10 mL, 0.069 mol) over 25 min at such a rate that the temperature was kept below 50 °C. The mixture was stirred at r.t. for 15 min until gas evolution ceased and then excess trimethyl phosphite was evaporated in vacuo leaving behind a white solid which could be recrystallized from Et_2O, or from benzene/petroleum ether (bp 40–60 °C); yield: 14.9 g (78%); mp 78–80 °C.
^{1}H NMR ($CDCl_3$): δ = 8.0–7.6 (m, 4H, arom), 4.0 (d, 3H, J = 10.5 Hz, CH_3OP), 3.70 (d, 3H, J = 10.5 Hz, CH_3OP).
^{31}P NMR ($CDCl_3$): δ = 7.9 (septet, J = 10.5 Hz).

Synthesis of *N*-Phthaloylamines 2; General Procedure:
Method A: To **1** (0.7 g, 2.5 mmol) dissolved in MeCN (25 ml), was added an amine (2.8 mmol) and Et_3N[14] (282 mg, 2.8 mmol). After 10 min ^{31}P NMR showed complete conversion of **1** to dimethyl phosphite. The mixture was evaporated in vacuo (50 °C/0.026 mbar), the residue dissolved in CH_2Cl_2 (50 mL), washed with sat. $NaHCO_3$ (2 × 20 mL), dried (Na_2SO_4) and evaporated in vacuo. The phthalimide was recrystallized from MeOH.
Method B: To **1** (1.38 g; 5 mmol) and the amine (5.25 mmol) dissolved in MeCN/H_2O (1:1, 25 mL) was added *i*-Pr_2NEt (3.5 mL, 20 mmol) and the mixture stirred at r.t. After 10 min ^{31}P NMR showed complete conversion of **1** to dimethyl phosphite. The mixture was concentrated in vacuo to a small volume (50 °C/0.026 mbar), acidified with 2 M HCl, and cooled to 0 °C. The white precipitate was filtered, washed with ice cold 2 M HCl and dried in vacuo over P_2O_5.

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