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Synthesis of 2(1*H*)-Pyrazinone Phosphonates via an Arbuzov-type Reaction

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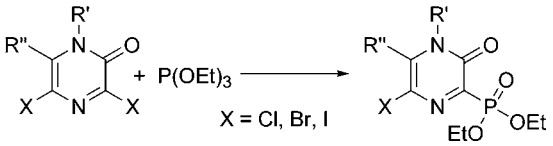

A simple and catalyst-free method for the synthesis of phosphonated 2(1*H*)-pyrazinones is described starting from 3,5-dichloropyrazinones. The method also works for 3-bromo- and 3-iodopyrazinones. Classical heating conditions as well as microwave-enhanced reaction conditions were tested.

2(1*H*)-Pyrazinones constitute an important class of compounds, as they are versatile building blocks in organic synthesis both as templates and as starting materials for heterocycle construction.[1] Some of these scaffolds show very promising activity as μ-opioid receptor agonists,[2] NNRTI's (non-nucleoside reverse transcriptase inhibitors),[3] and selective tissue factor VIIa inhibitors.[4] Very recently, 2(1*H*)-pyrazinone-incorporated nucleoside analogues (Figure 1) have been reported as antiviral agents for the treatment of flaviviruses, pestiviruses, and hepaciviruses and, in particular, of hepatitis C infection.[5] Furthermore, the 2-azadiene system of the pyrazinone skeleton easily undergoes an inter- or intramolecular Diels−Alder reaction with ethylene to afford bicyclic products which provide access to various scaffolds of pharmaceutical interest such as β-turn mimics.[6]

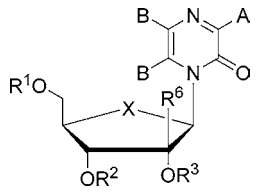

FIGURE 1. 2(1*H*)-Pyrazinone containing nucleoside analogue with antiviral properties.

Introduction of phosphorus functionalities has been shown to increase the activity of a number of pharmaceuticals.[7] Moreover, dialkyl (hetero)arylphosphonates[8] are currently being investigated as important intermediates in the synthesis of pesticides and biologically active compounds.[7b,9,10a] Therefore, we explored the Arbuzov reaction[10] with 3,5-dichloro-2(1*H*)-pyrazinones for generating a variety of 3-phosphonated pyrazinones, thus constituting a new class of dialkyl heteroarylphosphonates.[11] As far as we know, a pyrazinone containing a phosphorus substituent has not been reported to date.

Phosphonation reactions can be carried out in a number of ways, the Arbuzov reaction probably being the most classical one. This reaction proceeds via nucleophilic attack (S_N2) of $P(OEt)_3$ on an alkyl halide. The phosphonium salt formed in this way readily undergoes a C−O bond cleavage as the halide ion attacks one of the alkyl groups in a subsequent S_N2 reaction to yield a phosphonate ester. Besides (mostly primary) alkyl halides, acyl halides also undergo this reaction.[7d]

From our experience with 3,5-dichloropyrazinones, we know that the imidoylchloride functionality present in these molecules shows reactivity very similar to that of an acyl halide. Hence 3,5-dichloropyrazinones were chosen as starting materials for

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SCHEME 1. Reaction of Triethyl Phosphite with Various 3,5-Dichloro-2(1*H*)-pyrazinones 1a−i

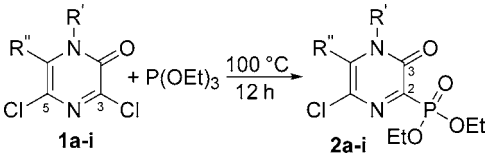

TABLE 1. Reaction of Triethyl Phosphite with Various 3,5-Dichloro-2(1*H*)-pyrazinones 1a−i

entry	R′	R″	product **2**	yield (%)
1	PMB	H	**a**	98
2	Bn	H	**b**	74
3	*t*-Bu	H	**c**	66
4	*o*-NO_2Bn	H	**d**	traces
5	PMB	Me	**e**	82
6	$(CH_2)_5$SePh	Me	**f**	92
7	Ph	Ph	**g**	96
8	Me	PhEt	**h**	94
9	-CH_2-CH_2-CH_2-		**i**	78

our phosphonation attempts to generate the phosphonated heterocycles. Moreover, these systems are easily accessible from cheap starting materials and allow a diverse substitution pattern. This is illustrated by the fact that over 50 dichloropyrazinones are reported up to now,[1] most of which can be synthesized in a yield of over 75% by reaction of an α-aminonitrile with oxalylchloride.[12] For this specific study, compounds **1a**−**i** were selected as starting materials (Scheme 1). The novel, bicyclic dichloropyrazinone **1i** was synthesized via a new procedure starting from prolinamide, and it was characterized via NMR and single-crystal X-ray analysis (the procedure for the synthesis of this compound and the X-ray structure can be found in the Supporting Information).

Our first attempt to generate the phosphonated pyrazinone using an Arbuzov-type procedure was immediately successful; as we expected, the reactive imidoylchloride moiety in the 3-position of 2(1*H*)-pyrazinone **1a** easily underwent the desired substitution upon heating the material at 100 °C under an inert atmosphere in triethyl phosphite as the solvent (Scheme 1). The reaction was completed in 12 h, affording the pyrazinone phosphonate **2a** in an excellent yield of 98% (Table 1, entry 1). Spectroscopic data were in agreement with the assigned structure of compound **2a**. Mass spectrometry shows a clear molecular ion peak, which shows only one chlorine atom was substituted. The lactam carbonyl carbon atom at $\delta_C = 153.8$ ppm appears as a doublet with a coupling constant, $^2J_{PC}$, of 31 Hz, demonstrating that phosphorus is attached to C-2, as could be expected.[13] Additionally the ^{13}C NMR spectrum shows an absorption at $\delta_C = 148.3$ ppm as a doublet with a coupling constant $^1J_{PC} = 229$ Hz for the carbon directly bonded to the phosphorus atom (C-2) and doublets at 125.9 ppm (C-6) and 130.8 ppm (C-5) with corresponding coupling constants $^3J_{PC} = 28$ Hz and $^4J_{PC} = 2$ Hz, respectively.

It is noteworthy that this method does not require the use of a catalyst, whereas in most cases, the synthesis of (hetero)-arylphosphonates cannot be performed without a suitable metal complex.[8a−e]

TABLE 2. Influence of Microwave Irradiation on the Arbuzov-type Reaction

entry	R′	R″	product **2**	yield mw (%)[a]	yield hp(%)[b]
1	PMB	H	**a**	85	98
2	PMB	Me	**e**	59	82
3	Ph	Ph	**g**	90	96

[a] Isolated yield of purified product upon microwave heating (mw). [b] Isolated yield of purified product upon conventional heating on a heating plate (hp).

To evaluate the general use of the reaction, a number of pyrazinones with different substituents R′ and R″ were subjected to the same reaction conditions (Scheme 1 and Table 1, entries 2−9), affording the desired phosphonates in moderate to good yields in most cases. When R′ is an *o*-nitrobenzyl group (Table 1, entry 4), formation of the pyrazinone phosphonate **2d** was observed by mass spectroscopy, but the amount was too small to be isolated. It is known from literature that side reactions may occur in the Arbuzov reaction when a nitro functionality is present.[7d]

Product **2c** (Table 1, entry 3) could be isolated in a satisfying yield of 66%, taking into account the lability of the *t*-Bu substituent on N-1 in the starting material.[14]

Since, in the course of the past years, microwave chemistry[15] has proven its usefulness in both the Arbuzov reaction[16] and as the decoration of our pyrazinone scaffolds,[17] we decided to investigate the influence of microwave irradiation on this Arbuzov-type reaction. Representative reactions were performed in a mono-mode microwave reactor that enables rapid heating of reaction mixtures in sealed vials under controlled conditions with simultaneous monitoring of real-time pressure and temperature. Using a maximum power of 150 W, pyrazinones **1a**,**e**,**g** were stirred at 100 °C for 20 min with excess triethyl phosphite, resulting in complete conversion of the starting material in the cases of **1a**, **1e**, and **1g**. This represents a dramatic shortening of the reaction time compared to the 12 h required under conventional heating at the same temperature.[18] The isolated yields of **2a**,**g** are only slightly lower than those obtained under conventional heating conditions (Table 2) due to an apparent promotion of side reactions upon microwave irradiation (as seen in TLC). The decrease in yield is more pronounced in the case of **1e**, yet the isolated yield is still satisfactory (Table 2, entry 2).

In order to check the scope of the method, the Arbuzov-type reaction of triethyl phosphite with 3,5-dibromo-2(1*H*)-pyrazinone **3**[19] was carried out (Scheme 2). Phosphonate **4** was obtained in 48% yield, as confirmed by NMR spectroscopy.

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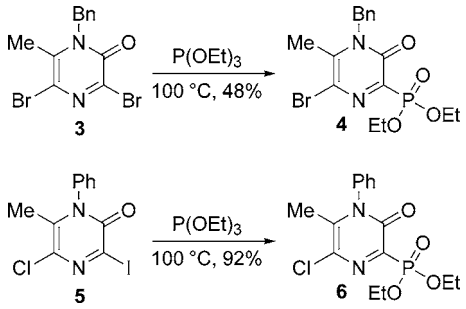
(19) See ref 3 for the synthesis of the 3,5-dibromopyrazinone.

SCHEME 2. Substitution of 3,5-Dibromo- and 5-Chloro-3-iodo-2(1*H*)-pyrazinones with Triethyl Phosphite



Finally, the iodine atom at the 3-position of **5**[20] was also substituted by the phosphorus reagent, affording the 5-chlorophosphonated heterocycle **6** in 92% yield (Scheme 2).

In conclusion, the first synthesis of pyrazinones containing a phosphonate group is described, starting from easily accessible starting materials. The imidoylchloride moiety of the 3,5-dichloropyrazinones is substituted using the Arbuzov-type reaction, affording the monochlorinated product, mostly in good to excellent yields. Moreover we have demonstrated that imidoylbromide and iodide moieties are equally prone to substitution with the phosphorus species. Microwave irradiation reduces the reaction time dramatically, yet at the same time, it also induces side reactions, resulting in slightly to moderately decreased yields. The resulting phosphorylated pyrazinones may be important building blocks for the preparation of a number of biologically active compounds.[6,7b,9]

Experimental Section

Typical Experimental Procedure for the Arbuzov-type Reaction of Pyrazinones with Triethyl Phosphite under Conventional Heating. Pyrazinone **1a** (0.3 mmol) was stirred in 7 mL of triethyl phosphite for 12 h at 100 °C under an inert atmosphere. After completion of the reaction, excess triethyl phosphite was evaporated. The crude product was purified by column chromatography over silica gel using dichloromethane/methanol (97:3) as the eluent to give pyrazinone phosphonate **2a**. Spectral data for product **2a**: Yield 98%; IR (NaCl, cm^{-1}) 1658, 1578; ^1H NMR ($CDCl_3$, 300 MHz, δ) 7.64 (s, 1H), 7.35 (d, 2H, $J = 8.0$ Hz), 6.88 (d, 2H, $J = 8.1$ Hz), 5.07 (s, 2H), 4.36 (m, 4H), 3.79 (s, 3H), 1.39 (t, 6H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 159.5, 153.8 (d, $J = 31$ Hz), 148.3 (d, $J = 229$ Hz), 130.8 (d, $J = 2$ Hz), 130.1, 125.9 (d, $J = 28$ Hz), 125.5, 113.9, 63.6 (d, $J = 6$ Hz), 54.7, 51.6, 15.8 (d, $J = 6$ Hz); EIMS *m*/*z* (%) 386 (M+, 24), 121(100); HRMS calcd for $C_{16}H_{20}ClN_2O_5P$, 386.0798; found, 386.0796.

Typical Experimental Procedure for the Arbuzov-type Reaction of Pyrazinones with Triethyl Phosphite under Microwave Irradiation. Pyrazinone **1a** (0.15 mmol) was put in a 10 mL glass vial equipped with a small magnetic stirring bar. To this was added triethyl phosphite (3 mL), and the vial was tightly sealed with an aluminum/Teflon crimp top. The mixture was then irradiated for 20 min at 100 °C using an irradiation power of 150 W. After completion of the reaction, the vial was cooled to 50 °C by gas-jet cooling before it was opened. After evaporation of the solvent, the crude product was purified by column chromatography over silica gel using dichloromethane/methanol (97:3) as the eluent, to give pyrazinone phosphonate **2a**. Yield: 85%.

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Supporting Information Available: General procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The 5-chloro-3-iodopyrazinone was synthesized according to a procedure described in: De Borggraeve, W. M. Ph.D. Thesis, Katholieke Universiteit Leuven, 2002.