***SHORT PAPER***

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# A convenient synthesis of α-ureidomethylphosphonates with heterocycle moiety†

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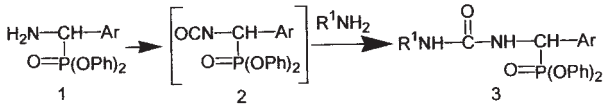
Some novel heterocycle-substituted α-ureidoalkylphosphonates **3** have been synthesised through the reaction of α-isocyanatoalkylphosphonates with heterocyclic amines.

**Keywords:** phosphonate esters, ureas, isocyanates, α-aminophosphonates

As isosteres of aminocarboxylic acids, α-aminoalkylphosphonic acid derivatives have attracted an increasing amount of attention in the past two decades because some of them are of considerable chemical and pharmacological importance.[1] Some derivatives of α-aminoalkylphosphonic acid can also serve in agrochemistry as fungicides,[2] herbicides,[3] plant regulators[4] and plant virucides.[5] In our previous work, we have synthesised two series of α-aminoalkylphosphonates with pyrazole[6] or benzothiazole[7] moiety, which showed significant anti-TMV (tobacco mosaic virus) activity. As part of our ongoing program and interesting in the development of new biologically active organophosphorus compounds, we decided to synthesise some N′-heterocycle-substituted α-ureidoalkylphosphonates **3**.

The general method for synthesis of substituted α-ureidoalkylphosphonates is the three component reaction of substituted ureas, aldehydes (ketones) and trivalent phosphorus compounds.[8,9] Since the synthetic methods and reactivity of different heterocycle-substituted ureas are variable, the synthesis of **3** by a three-component reaction can be laborious and unpredictable. In this article we report a convenient method for the synthesis of substituted α-ureidoalkylphosphonates **3** (Scheme 1).




**Scheme 1**

The easily available α-aminoalkylphosphonates **1**[10] were treated with triphosgene to give **2** in mild conditions. Because they are very sensitive to moisture, the isocyanates **2** were not purified and their presence was revealed by their characteristic IR absorption, the very strong band of N=C=O at approximately 2240 $cm^{-1}$. To accomplish the complete conversion of **1** into **2** a slight excess of triphosgene was used. Through further addition of 0.85 molar of heterocyclic amines to **2** in one pot, **3** were obtained in good to high yields. The structures and physical data of compounds **3** are listed in Table 1.

The preparation of **3** by treating **1** with heterocyclic isocyanates $R^1NCO$ seems applicable, but attempts to obtain various $R^1NCO$ under a unique set of reaction conditions proved to be unsuccessful.

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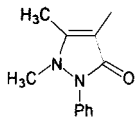
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

**Table 1** The structures and physical data of **3a–3h**

| No. | Ar | $R^1$ | yield/% | m.p./°C |
|---|---|---|---|---|
| **3a** | Ph | 2-pyridyl | 81 | 150–152 |
| **3b** | 2-$ClC_6H_4$ | 4-antipyryl* | 58 | 101–103 |
| **3c** | 3-$NO_2C_6H_4$ | 4-antipyryl | 40 | 96–98 |
| **3d** | Ph | 4-antipyryl | 67 | 92–94 |
| **3e** | Ph | 4,6-dimethyl-2-pyrimidyl | 73 | 120–122 |
| **3f** | 2-$ClC_6H_4$ | 4,6-dimethoxy-2-pyrimidyl | 61 | 149–151 |
| **3g** | Ph | 2-benzothiazolyl | 69 | 168–170 |
| **3h** | 2-$ClC_6H_4$ | 2-thiazolyl | 82 | 167–169 |

*4-antipyryl:




## Experimental

α-Aminoalkylphosphonates **1**[10] and triphosgene[11] were prepared according to reported procedures.

*Diphenyl aryl(N³-heterocyclylureido)methylphosphonates* (**3a–h**): To a solution of triphosgene (1.78 mmol) in 5ml dichloromethane, a solution of α-aminoalkylphophonate **1** (3.68 mmol) and triethylamine (18 mmol) in 10ml dichloromethane was added dropwise below –10 °C during 30 minutes. The resulted mixture was stirred for additional 30 minutes at –10 °C and warmed spontaneously to room temperature, then a solution of heterocyclic amine (3.13 mmol) in 15 ml dichloromethane was added. The solvent was removed under vacuum after the mixture stirred at room temperature for 3 hours. The residue was dissolved in ethyl acetate and filtered, then the filtrate was evaporated and purified by chromatography on silica gel to give **3** as a white solid. The structures of the substituents in the products **3**, and their melting-points and yields, are listed in Table 1.

**3a**: $^1$H NMR (δ, ppm): 6.00(q, 1H), 6.75–8.25(m, 19H), 9.26(s, 1H), 10.76(br, 1H). $^{13}$C NMR (δ, ppm): 51.5(d, *J*=156Hz), 112.5, 117.0, 120.4, 125.0, 128.1, 128.5, 129.4, 134.6, 138.6, 145.3, 150.3, 152.7, 155.7. IR (ν/$cm^{-1}$): 767, 939, 1183, 1207, 1488, 1561, 1591, 1684, 3222, 3403. MS($M^+$ 459): 366, 285, 233, 226, 209, 132, 131, 106(100%), 77. Found: C, 65.31; H, 4.95; N, 9.13%. $C_{25}H_{22}N_3O_4P$ requires C, 65.36; H, 4.83; N, 9.15%.

**3b**: $^1$H NMR (δ, ppm): 2.17(s, 3H), 3.01(s, 3H), 6.33(dd, 1H), 6.95–7.50(m, 19H), 7.82(br, 1H), 8.15(br, 1H). $^{13}$C NMR (δ, ppm): 11.5, 35.4, 48.4(d, *J*=160Hz), 109.0, 120.3, 120.7, 125.0, 127.3, 127.7, 129.4, 133.1, 133.5, 148.3, 150.3, 155.9, 160.1. IR (ν/$cm^{-1}$): 758, 933, 1180, 1206, 1487, 1588, 1623, 1696, 3050, 3306. MS($M^+$ 602): 508, 473, 352, 276, 229, 213, 166, 140, 94, 77, 56(100%). Found: C, 61.45; H, 4.56; N, 9.00 %. $C_{31}H_{28}ClN_4O_5P$ requires C, 61.75; H, 4.60; N, 9.29%.

**3c**: $^1$H NMR (δ, ppm): 2.20(s, 3H), 3.08(s, 3H), 5.78(dd, 1H), 7.05–8.52(m, 19H), 8.56(br, 1H). Found: C, 60.62; H, 4.69; N, 11.15%. $C_{31}H_{28}N_5O_7P$ requires C, 60.69; H, 4.60; N, 11.41%.

**3d**: $^1$H NMR (δ, ppm): 2.12(s, 3H), 2.94(s, 3H), 5.83(dd, 1H), 6.96–7.33(m, 20H), 7.75(br, 1H), 8.13(s, 1H). Found: C, 65.42; H, 5.30; N, 9.87%. $C_{31}H_{29}N_4O_5P$ requires C, 65.49; H, 5.14; N, 9.85%.

**3e**: $^1$H NMR (δ, ppm): 2.38(s, 6H), 5.87(q, 1H), 6.62(s, 1H), 6.93–7.54(m, 15H). Found: C, 63.79; H, 5.31; N, 11.56%. $C_{26}H_{25}N_4O_4P$ requires C, 63.93; H, 5.16; N, 11.47%.

**3f**: $^1$H NMR (δ, ppm): 3.91(s, 6H), 5.68(s, 1H), 6.50(q, 1H), 6.80–7.60(m, 14H). MS ($M^+$ 554): 461, 321, 306, 182, 166, 154, 140(100%), 94, 77. Found: C, 56.25; H, 4.39; N, 10.03%. $C_{26}H_{24}ClN_4O_6P$ requires C, 56.28; H, 4.36; N, 10.10%.

**3g**: $^1$H NMR (δ, ppm): 5.81(q, 1H), 6.90–7.92(m, 19H), 8.38(d, 1H), 10.55(br, 1H). Found: C, 62.93; H, 4.45; N, 8.21%. $C_{27}H_{22}N_3O_4PS$ requires C, 62.91; H, 4.30; N, 8.15%.

**3h**: $^1$H NMR (δ, ppm): 6.53(q, 1H), 6.81–7.46(m, 16H), 7.97(br, 1H), 9.90(br, 1H). Found: C, 55.00; H, 3.96; N, 8.36%. $C_{23}H_{19}ClN_3O_4PS$ requires C, 55.26; H, 3.83; N, 8.41%.

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