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First synthesis of 2-[alkylamino(diethoxyphosphoryl)methyl]acrylic ethyl esters

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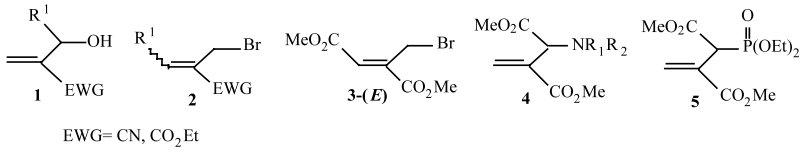
Abstract—The ethyl α-bromomethyl-β-(diethoxyphosphoryl)acrylic acid ester **9** has been prepared by addition of bromine to allylphosphonate **7** then dehydrobromination with DBU in acetonitrile. Reaction of allylic bromide **9** with primary amines in a bimolecular S_N2'-type mechanism in methanol at low temperature, gives rise to the 2-[alkylamino(diethoxyphosphoryl)methyl]acrylic acid ethyl esters **6**.

In recent years numerous methods have been developed to prepare α-functionalized acrylic esters, ketones and nitriles[1–8] in response to a number of synthetic objectives[9–14]. Since 1972, a number of ongoing synthetic efforts[15] for introduction of further separated functionality (e.g. alkylamino[16,17] and dialkoxyphosphoryl[18,19] groups) have been widely documented (Scheme 1).

The 'bromide' version of the reaction, i.e. exchanging the hydroxyl group for a bromomethyl one, has been achieved by treatment of α-(1-hydroxyalkyl)acrylic compounds **1** with phosphorus tribromide in diethyl ether at 0°C, leading respectively to allylic bromide **2** as a mixture of *E*,*Z*-isomers in which *E*-isomers is strongly predominant (EWG = CN) and exclusively the *Z*-isomers when EWG = COOEt.[20] In a previous paper, we described a simple and convenient synthesis of dimethyl α-(bromomethyl)fumarate **3**[21] and we have demonstrated that **3** can be utilized as an electrophilic reagent for access to some α-(*gem*-difunctional methyl)acrylic acid esters **4**[22] and **5**.[23]

In light of our previous studies on the reaction of α-(bromomethyl)acrylic acid ester **2** ($R^1 = H$), we report herein a convenient procedure for the preparation of analogous compound **5** where the methoxy carbonyl group was changed into an amino one leading to new functionalized allylamines **6** (Scheme 2).

The synthesis started from allylphosphonate **7**,[19] which was subjected to the reaction of bromine in carbon tetrachloride leading to the intermediate **8**. Through a selective dehydrobromination using DBU in acetonitrile, the latter afforded crude product which was mixed with silicagel then was flash chromatographed. This led to the *Z* ethyl α-(bromomethyl)-β-diethoxyphosphoryl acrylic ester **9** in good yields;[24] its configuration was elucidated on the basis of a NOESY correlation for H_a (δ 6.8) and H_b (δ 1.37) (Scheme 3). Finally, upon stirring **9** in methanol, primary amines (2 equiv.) react in a clean S_N2' reaction, giving **6** in moderate yields[25] as indicated in Table 1. The (*Z*)-selectivity of the reaction formation of compound **9** from **8** may be explained by the strike bulkiness factor of the ethoxycarbonyl group



Scheme 1.

Keywords: dimethyl α-(bromomethyl)fumarate; 2-[alkylamino(diethoxyphosphoryl)methyl]acrylic acid esters.
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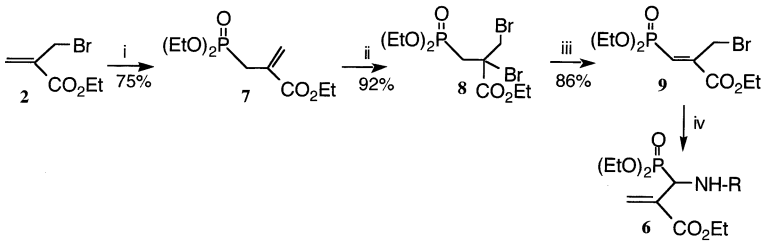
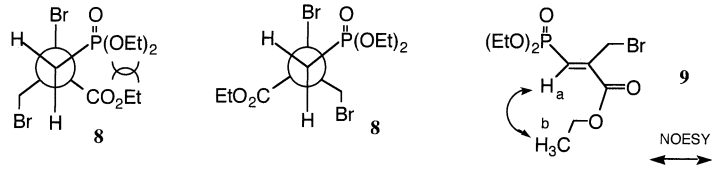


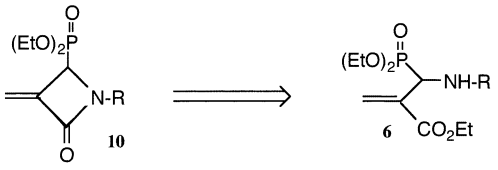
Scheme 2. (i) $(EtO)_2P(O)Na$, THF, −78°C; (ii) Br_2, CCl_4, reflux; (iii) DBU, CH_3CN, rt; (iv) R-NH_2, MeOH, 0°C.



Scheme 3.

Table 1. Synthesis of 2-[alkylamino(diethoxyphosphoryl)-methyl]acrylic ethyl esters **6**

Product	R	Time (h)	Yield (%)
6a	^{n}Pr	6	35
6b	^{i}Pr	5	65
6c	^{n}Bu	6	30
6d	^{s}Bu	6	76
6e	^{p}MeO-C_6H_4-CH_2	5	45
6f	^{p}F-C_6H_4-CH_2	5	50
6g	C_6H_5-CH_2	7	58
6h	$^{c}C_6H_{11}$	6	68



Scheme 4.

in the β-elimination step in which Br and H are antiperiplanar (Scheme 3).

In summary, we have developed an efficient and simple synthesis of 2-[alkylamino(diethoxyphosphoryl)methyl]-acrylic esters **6** which constitute intermediates of choice to reach α-methylene-β-functional azetidinones **10** through a tandem: hydrolysis–intramolecular lactamization[26–28] (Scheme 4). This investigation will be the subject of our future report.

References

1. Villiéras, J.; Rambaud, M. *Synthesis* **1982**, 924–926.
2. (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795–796; (b) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849–3859; (c) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110.
3. Basavaiah, D.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1986**, *27*, 2031–2032.
4. Amri, H.; Villiéras, J. *Tetrahedron Lett.* **1986**, *27*, 4307–4308.
5. Basavaiah, D.; Bharathi, T. K.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1987**, *28*, 4351–4352.
6. Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K. *Tetrahedron Lett.* **1987**, *28*, 4591–4592.
7. Beltaïef, I.; Amri, H. *Synth. Commun.* **1994**, *24*, 2003–2010.
8. Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971–6976.
9. El Alami, N.; Belaud, C.; Villiéras, J. *Tetrahedron Lett.* **1987**, *28*, 59–60.
10. Amri, H.; Rambaud, M.; Villiéras, J. *Tetrahedron Lett.* **1989**, *30*, 7381–7382.
11. Amri, H.; Rambaud, M.; Villiéras, J. *Tetrahedron Lett.* **1990**, *46*, 3535–3546.
12. Bauchat, P.; Le Rouillé, E.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1991**, 267–271.
13. El Alami, N.; Belaud, C.; Villiéras, J. *Synthesis* **1993**, 1213–1214.
14. Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375–378.
15. Baylis, A. B.; Hillman, M. E. D. German Patent 2,155,113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.
16. Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr.* **1989**, 403–408.
17. Hbaïeb, S.; Latiri, Z.; Amri, H. *Synth. Commun.* **1999**, *29*, 981–988.
18. Basavaiah, D.; Pandiaraju, S. *Tetrahedron* **1996**, *52*, 2261–2268.
19. Fields, S. C. *Tetrahedron Lett.* **1998**, *39*, 6621–6624.
20. Beltaïef, I.; Hbaieb, S.; Besbes, R.; Amri, H.; Villiéras, M.; Villiéras, J. *Synthesis* **1998**, 1765–1768.

21. Besbes, R.; Villiéras, M.; Amri, H. *Indian J. Chem*. **1997**, *36B*, 5–8.
22. Ben Gharbia, S.; Besbes, R.; Villiéras, J.; Amri, H. *Synth. Commun*. **1996**, *26*, 1685–1692.
23. Béji, F.; Lebreton, J.; Villiéras, J.; Amri, H. *Synth. Commun*. **2002**, *32*, 3273–3278.
24. *Synthesis of ethyl α-(bromomethyl)-β-diethoxyphosphoryl acrylic acid ester* ***9***: A solution of bromine (52 mmol) in carbon tetrachloride (20 mL) was added dropwise to a refluxing solution of allylphosphonate **7** (50 mmol) in carbon tetrachloride (100 mL) at such a rate that the bromine color gradually disappeared. The end of the reaction is indicated by the persistence of a brownish color. Excess of bromine was removed by washing with aqueous solution of sodium thiosulfate. The organic layer was then washed with brine and dried over magnesium sulfate. Filtration and removal of the solvent gave a residue **8**. DBU (50 mmol) was added at rt to a solution of **8** in acetonitrile (250 mL). The mixture was stirred for 12 h at rt, then silica gel (12 g) was added and the solvent was evaporated. The residue, consisting of crude silica gel, was flash chromatographed, using a suitable ratio of ethyl acetate/methylene chloride as eluent, affording the pure compound **9**. Spectroscopic data: ^{1}H NMR (300 MHz, $CDCl_3$): 1.35 (t, 6H, $J=7.3$ Hz), 1.37 (t, 3H, $J=7$ Hz), 4.20 (q, 4H, $J=7.3$ Hz), 4.30 (q, 2H, $J=7$ Hz), 4.70 (s, 2H), 6.8 (d, 1H, $J=13.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 13.8 (CH_3), 16.3 (CH_3), 24.2 (CH_2Br), 62.3 (CH_2O), 62.6 (CH_2O), 126.0 (=CH, $J_{C-P}=182.5$ Hz), 146.1 (=C), 164.4 (COO). MS (EI) m/z: 330 (M^++2, 22), 328 (M^+, 20), 257 (15), 255 (13), 228 (69), 226 (68), 120 (38), 39 (45), 29 (100). IR (film) cm^{-1}: 1722.5, 1621.4.
25. *Typical procedure for the synthesis of 2-[alkylamino(diethoxyphosphoryl)methyl]acrylic acid ethyl ester* **6**: To a stirred solution of vinyl phosphonate **9** (1.64 g, 5 mmol) in methanol (10 mL) was added a solution of a *sec*-butylamine (0.73 g, 10 mmol) in methanol (3 mL) was added at 0°C. The mixture was stirred at 0°C for 6 h, then it was concentrated in order to partially remove MeOH. Chromatography on silica gel of the residue using ethyl acetate gave 2-[*sec*-butylamino(diethoxyphosphoryl)-methyl]acrylic acid ethyl ester **6d**. Spectroscopic data: ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (t, 3H, $J=7.3$ Hz), 0.97 (d, 3H, $J=6.2$ Hz), 1.29 (t, 3H, $J=7$ Hz), 1.32 (t, 6H, $J=7.3$ Hz), 1.37 (m, 2H), 1.83 (br. s, 1H, NH), 2.52 (m, 1H), 4.06 (q, 2H, $J=7$ Hz), 4.2 (q, 4H, $J=7.3$ Hz), 4.35 (d, 1H, $J=24.2$ Hz), 5.52, 6.45 (2t, 2H, $J=4.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 10.4 (CH_3), 14.2 (CH_3), 16.4 (CH_3), 19.1 (CH_3), 30.3 (CH_2), 51.2 (CHPO, $J_{C-P}=155.4$ Hz), 51.5 (CHN) 61.0 (CH_2O), 63.2 (CH_2O), 126.9 (=CH_2), 137.2 (=C), 166.1 (COO). MS (EI) m/z: (M^+, 7), 292 (9), 146 (14), 184 (100), 128 (15), 82 (30). IR (film) cm^{-1}: 1712.3, 1626.9.
26. Buchholz, R.; Hoffmann, H. M. R. *Helv. Chem. Acta* **1991**, *74*, 1213–1220.
27. Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett*. **1987**, *28*, 4335–4338.
28. Amri, H.; El Gaied, M. M.; Ben Ayed, T.; Villiéras, J. *Tetrahedron Lett*. **1992**, *33*, 6159–6160.