Facile Syntheses of α,α-Difluoro-β-ketophosphonates

Thierry P. Lequeux and Jonathan M. Percy*

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT

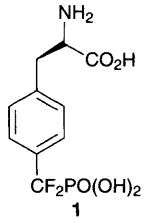
The cerium-mediated reaction between lithio (diethyldifluoromethyl)-phosphonate **2** proceeds smoothly to afford good yields of ketophosphonates; the reaction with DMF led to the formation of the corresponding aldehyde which was isolated as a hydrate with interesting and useful properties.

In some cases, difluoromethylene phosphonates are effective chemical mimics of phosphate esters. The presence of the two fluorine atoms results in low pK_a[1] and pK_a[2] values for the free phosphonic acid, ensuring that the ionisation profile bears a close resemblance to that of the native phosphate monoester.[1] Since the initial discoveries were made in the area, the growth of controversy[2] has outstripped the development of new synthetic methods. The range of accessible targets (and therefore the amount of information concerning recognition processes) has therefore been rather restricted. Two important papers should help to clarify thinking in the area. The effectiveness of the mimicry may depend critically on the nature of the molecular recognition between the native phosphate and its receptor. Recently, Burke and co-workers[3] demonstrated that hexapeptides containing phosphotyrosine analogue **1** (F_2Pmp) bound to Protein Tyrosine Kinase SH-2 domains as efficiently as the native phosphopeptide. The recent publication of a crystal structure of the complex formed between a phosphopeptide and a mutant Protein Tyrosine Phosphatase 1B enzyme revealed[4] one possible reason for the effectiveness of the chemical mimicry in this important biochemical system. The phenolic oxygen which bears the posphoryl group appears to be hydrogen bonded to a molecule of water of crystallisation alone, and to none of the components of the phosphate binding array directly. The substitution of a CF_2 group for this oxygen atom therefore compromises none of the important interactions in the phosphate-binding pocket.

During the course of our synthetic studies directed towards the synthesis of analogues of nucleoside 3′-phosphates, we discovered that conjugate additions of lithio (diethyldifluoromethyl)-phosphonate **2** to nitroalkenes occurred smoothly when cerium(III) chloride was present in the reaction mixture.[5] More recently, we have discovered that the cerium method allows the facile synthesis of α,α-difluoro-β-ketophosphonates in good yield. Compounds of this type are of interest[6,7] as potential mimics of reactive acyl phosphates, which are used as intermediate electrophiles in a number of enzyme-catalysed processes. The literature routes to compounds of this type involve the direct reaction of **2** with aroyl chlorides,[8] or the more general (but slower) reaction of zinc reagent **3** with the same electrophiles.[9] A significant disadvantage of both methods lies in the fact that they require the use of an acid chloride electrophile, limiting the range of other functional groups that can be present.

Our method (Scheme 1) uses ethyl ester electrophiles and short reaction times.† Slow addition of **4** to a solution of LDA and dry‡ cerium(III) chloride in THF at −78 °C and stirring the mixture for 1 h was followed by the addition of the ester. Further stirring (1 h) and an acidic quench at low temperature led to the formation of ketophosphonates **5** in good yield. Table 1 shows the range of compounds prepared using this method. When ethyl acrylate was used as the electrophile, 1,4-addition competed with ketoester formation. Several attempts to open β-propiolactone led to the formation of multiple (> 10) products and the reaction failed with *N,N*-dimethylacrylamide. However, with DMF,[10] an electrophile which fails[8] to yield useful products when exposed to **2**, we obtained an interesting result (Scheme 2). After acid work-up, **6** was obtained in excellent yield (80%).[11] The hydrate underwent a Wadsworth–Horner–Emmons reaction with triethyl phosphonoacetate to afford (*E*)-alkenoate **7** in good yield. Stirring **6** with nitromethane and potassium fluoride in propan-2-ol followed by acidic work-up led to the isolation of **8** in good yield.§

This work was supported by European Community Network on Synthesis and Molecular Recognition of Selectively Fluori-



1

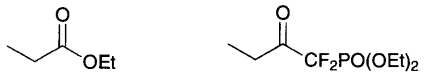
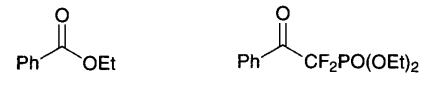
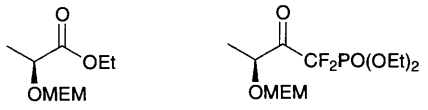
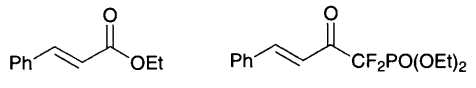
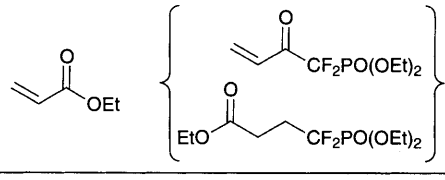
$LiF_2CPO(OEt)_2$ **2**

$BrZnF_2CPO(OEt)_2$ **3**

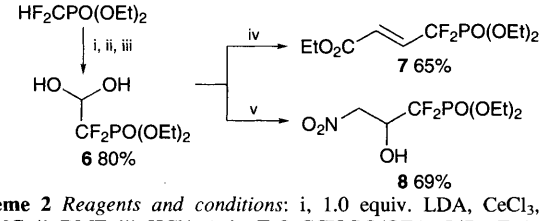
4 **5**

Scheme 1 *Reagents and conditions*: i, 1.0 equiv. LDA, $CeCl_3$, THF, −78 °C; ii, RCO_2Et; iii, HCl(aq)

Table 1

Electrophile	Product	Yield[a] (%) **5**
a		88
b		81
c		68
d		57
e		40[b]

[a] Yields refer to isolated yields of pure (> 98% by GC) products. [b] An inseparable 1 : 1 mixture of 1,2- and 1,4-adducts was isolated.



6 80% **7** 65% **8** 69%

Scheme 2 *Reagents and conditions*: i, 1.0 equiv. LDA, $CeCl_3$, THF, −78 °C; ii, DMF; iii, HCl(aq); iv, $EtO_2CCH_2PO(OEt)_2$, LiBr, Et_3N, THF, room temp. 2 h; v, $MeNO_2$, KF, propan-2-ol, room temp. 18 h

nated Bioactive Molecules (ERBCHRXCT930279). The authors also wish to thank the Royal Society for an equipment grant which allowed us to purchase a Gas Chromatograph.

Received, 10th July 1995; Com. 5/04527D

Footnotes

† *Typical procedure*: Butyllithium (4 ml of 1.4 mol dm^{-3} solution in hexanes, 5.6 mmol) was added dropwise to a cooled (−78 °C) solution of diisopropylamine (0.80 ml, 5.7 mmol) in dry THF (15 ml). The solution was warmed to 0 °C for 10 min under dry nitrogen. Freshly-dried cerium(III) chloride (1.3 g, 5.3 mmol) was added in one portion then the mixture was re-cooled to −78 °C and stirred vigorously at that temperature for 15–20 min. Neat **4** (1.00 g, 5.3 mmol) was added dropwise over 10–15 min and the mixture was stirred for 1 h. Then ethyl propionate (0.61 ml, 5.3 mmol) was added slowly to the pale yellow–orange suspension and after stirring for a further 1 h, an aqueous solution of HCl (3 mol dm^{-3}, 5 ml) was added. The stirred mixture was allowed to warm to room temp. over 20 min. The aqueous layer was extracted with dichloromethane (3 × 10 ml) and the combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Kugelrohr distillation afforded pure (>98%, GC) ketophosphonate **5a** (1.15 g, 88%) as a clear oil; bp 50–55 °C/0.1 mmHg; δ_H (300 MHz, $CDCl_3$) 4.15 (dq [appears as quintet], 4 H, $^3J_{HH}$ = 7, $^3J_{HP}$ = 7 Hz OCH_2CH_3), 2.55 (q, 2 H, $^3J_{HH}$ = 7 Hz, $OCCH_2CH_3$), 1.20 (t, 3 H, $^3J_{HH}$ = 7 Hz, OCH_2CH_3), 1.18 (t, 3 H, $^3J_{HH}$ = 7 Hz, OCH_2CH_3) and 0.95 (t, 3 H, $^3J_{HH}$ = 7 Hz, $OCCH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 199.1 (dt, $^2J_{CP}$ 14, $^2J_{CF}$ = 23 Hz, CO), 113.2 (dt, $^1J_{CP}$ = 195 Hz, $^1J_{CF}$ = 273 Hz, CF_2), 65.05 (d, $^2J_{CP}$ = 6.5 Hz, OCH_2CH_3), 30.8 (s, $OCCH_2CH_3$), 15.85 (d, $^3J_{CP}$ = 5 Hz, OCH_2CH_3) and 6.1 (s, $OCCH_2CH_3$); δ_F (84 MHz, $CDCl_3$, $CFCl_3$) −118.6 (d, 2 F, $^2J_{FP}$ = 94.9 Hz, CF_2); δ_P (36 MHz, $CDCl_3$) 3.2 (t, $^2J_{PF}$ = 94.9 Hz, P=O); MS (CI) *m/z* 262 ($M + NH_4^+$, 90%), 245 ($M + H^+$, 100), 208 (40), 206 (50) and 168 (15).

‡ Cerium chloride heptahydrate (Aldrich, 99%) was heated *in vacuo* (0.5 mmHg) to *ca.* 200 °C for 5 min, and again at intervals of 30 min over 2 h and then allowed to cool *in vacuo*.

§ We are exploring further the reaction with other active methylene compounds.

References

1 G. M. Blackburn, D. A. England and F. Kolkmann, *J. Chem. Soc., Chem. Commun.*, 1981, 930.
2 For example, see J. Nieschalk and D. O'Hagan, *J. Chem. Soc., Chem. Commun.*, 1995, 719. The most global statement in the area arose from a computational study: G. R. J. Thatcher and A. S. Campbell, *J. Org. Chem.*, 1993, **58**, 2272.
3 T. R. Burke, M. S. Smyth, A. Otaka, M. Nomizu, P. P. Roller, G. Wolf, R. Case and S. E. Shoelson, *Biochem.*, 1994, **33**, 6490.
4 Z. Jia, D. Barford, A. J. Flint and N. K. Tonks, *Science*, 1995, **268**, 1754.
5 T. Lequeux and J. M. Percy, *Synlett*, 1995, 361.
6 D. E. Rudisill and J. P. Whitten, *Synthesis*, 1994, 851.
7 S. D. Lindell and R. M. Turner, *Tetrahedron Lett.*, 1990, **31**, 5381.
8 G. M. Blackburn, D. Brown, J. Martins and M. J. Paratt, *J. Chem. Soc., Perkin Trans. 1*, 1987, 181.
9 D. J. Burton and L. G. Sprague, *J. Org. Chem.*, 1988, **53**, 1523.
10 E. Aboujoude, N. Collignon and P. Savignac, *Synthesis*, 1983, 634.
11 When acidic ethanol was used to quench the product mixture, the ethyl hemiacetal was isolated. Fluoroalkyl hemiacetals have shown a rich solution chemistry. T. Tsukamoto and T. Kitazume, *J. Chem. Soc., Chem. Commun.*, 1992, 540.