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Reactions of diethyl mesyl- or tosyloxyphosphonates with diethyl phosphite and base: a method claimed to yield bisphosphonates

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Abstract—Reactions of diethyl mesyl- or tosyloxyphosphonates with sodium diethyl phosphite in THF lead to the corresponding phosphono phosphates. Reaction of the mesyloxy derivative with diethyl phosphite in pyridine gives the phosphono phosphate as minor product. Neither method yields bisphosphonates. © 2002 Elsevier Science Ltd. All rights reserved.

In connection with a study[1] having as its goal the introduction of radioactive iodine into bone structures, one target molecule was tetraethyl *m*-iodobenzylidenebisphosphonate **1a**. 3-Nitrobenzaldehyde seemed a convenient starting material, particularly since Li and Yuan[2] have published what appeared to be a simple one-pot synthesis of tetraethyl bisphosphonates from aldehydes. The method involves condensation of diethyl phosphite with an aldehyde in pyridine solution to the corresponding hydroxyalkylphosphonate that without isolation, is transformed into the mesylate. Further reaction in the same pot with diethyl phosphite was reported to give excellent yields of bisphosphonates. However, subjecting 3-nitrobenzaldehyde to this protocol resulted in a complex product mixture, in which no detectable amount of the bisphosphonate **1b** was present. Starting from benzaldehyde we then attempted the synthesis of tetraethyl benzylidenebisphosphonate **1c** as described by Li and Yuan. The crude product consisted of a complex mixture of compounds, containing the phosphono phosphate **2a**[3] as a minor constituent, but none of the bisphosphonate **1c** as claimed. An authentic sample of the latter was prepared from diethyl benzylphosphonate according to the literature[4] and the physical and spectroscopic data differ significantly from those reported by Li and Yuan.[2]

On the other hand, the reaction of 3-nitrobenzaldehyde with diethyl phosphite using potassium fluoride as base and no solvent[5] furnished the hydroxyphosphonate **3a**[6] in almost quantitative yield. Treatment of the corresponding mesylate **3b** with sodium diethyl phosphite in THF afforded the phosphono phosphate **2b**[6] in 73% yield; by using the tosylate **3c** under the same reaction conditions the yield of **2b** was improved to 89%. Moreover, a similar reaction of the tosylate **4b** afforded the phosphono phosphate **2a** in 63% yield. No detectable amounts of the bisphosphonates **1b** and **1c**, respectively, were formed under these reaction conditions. The structure of compound **2b** was established by comparison of the spectral data with those of an authentic sample, prepared from **3a** and diethyl chlorophosphate.[7]

Creary and co-workers[8] have reported that solvolysis of the mesylate **4a** gave exclusively substitution products, derived from an intermediate carbocation. Our results appear anomalous, but the conditions should favour an S_N2 reaction, which is disfavoured by both a crowded benzylic carbon and a bulky nucleophile. Hence, another reaction path may become competitive, and we suggest the intermediate formation of the ketone **5**.[9] It is known to give a high yield of the phosphono phosphate **2a** with diethyl phosphite in the presence of a base,[10] a reaction involving the facile rearrangement of an initially formed hydroxybisphosphonate anion.[7] The ketone **5** may result from abstraction of the benzylic proton of the sulfonate esters, facilitated by the neighbouring diethylphosphonate group, followed by elimination of the sulfinate anion. Support for such an oxidation process comes from the work of Creary[11] who showed that similar reactions on triflates lead to ketones. Furthermore, when we treated the tosylate **4b** with sodium ethoxide in ethanol, one of the products was ethyl benzoate, indicating the intermediacy of the ketone **5**.[9]

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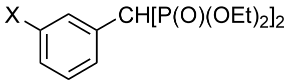
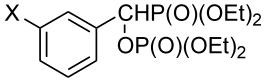
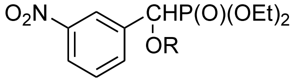


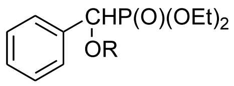
1a: X = I
b: X = NO_2
c: X = H



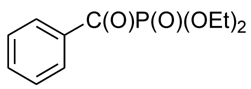
2a: X = H
b: X = NO_2



3 a: R = H
b: R = SO_2Me
c: R = SO_2-*p*-Tol



4a: R = SO_2Me
b: R = SO_2-*p*-Tol



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In conclusion, our results show that reactions of sulfonic esters with phosphite anion lead to phosphono phosphates, strongly indicating that the results of Li and Yuan[2] have been erroneously interpreted.

References

1. Årstad, E.; Hoff, P.; Skattebøl, L.; Skretting, A.; Breistøl, K. *J. Med. Chem.*, submitted.
2. Li, C.; Yuan, C. *Tetrahedron. Lett.* **1993**, *34*, 1515–1516.
3. Ruel, R.; Bouvier, J.-P.; Young, R. N. *J. Org. Chem.* **1995**, *60*, 5209–5213.
4. Teulade, M.-P.; Savignac, P.; Aboujaoude, E. E.; Lietge, S.; Collignon, N. *J. Organomet. Chem.* **1986**, *304*, 283–300.
5. Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 165–166.
6. Compound **3a**: mp 93–95°C. IR (KBr): 3750–3040, 1540, 1355, 1205, 1050; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (6H, m), 4.10 (4H, m), 5.14 (1H, d, $J=12$ Hz), 5.94 (1H, s, OH) and 7.93 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.6, 64.2, 64.9, 72.1, 122.4, 123.1, 129.3, 133.4, 139.8 and 148.3; HR-MS (EI): *m*/*e* 289.0715 (M^+ $C_{11}H_{16}NO_6P$ requires 289.0714). Compound **2b**: pale yellow coloured oil; IR (film): 2910, 1535, 1350, 1290, 1025; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (12H, m), 3.99 (8H, m), 5.64 (1H, dd, $J=3$, 11 Hz) and 7.87 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.6 (m), 64.5 (m), 71.9 (d, $J=7$ Hz), 75.3 (d, $J=7$ Hz), 122.5, 123.8, 128.4, 129.5, 133.7 and 148.3; HR-MS (EI): *m*/*e* 425.1010 (M^+ $C_{15}H_{25}NO_9P_2$ requires 425.1006).
7. Pudovik, A. N.; Zimin, M. G. *Pure Appl. Chem.* **1980**, *52*, 989–1011 and references cited therein.
8. Creary, X.; Geiger, C. C.; Hilton, K. *J. Am. Chem. Soc.* **1983**, *105*, 2851–2858.
9. Terauchi, K.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 883–890.
10. Okamoto, Y.; Sakurai, H. *Kogyo Kagaku Zasshi* **1968**, *71*, 310–311.
11. Creary, X. *J. Org. Chem.* **1980**, *45*, 2419–2425.