Pergamon

Tetrahedron Letters 42 (2001) 8071–8073

TETRAHEDRON LETTERS

Lithium perchlorate/diethyl ether catalyzed one-pot synthesis of α-hydrazinophosphonates from aldehydes by a three-component reaction†

Akbar Heydari,[a,*] Abdollah Javidan[b] and Mehdi Schaffie[a]

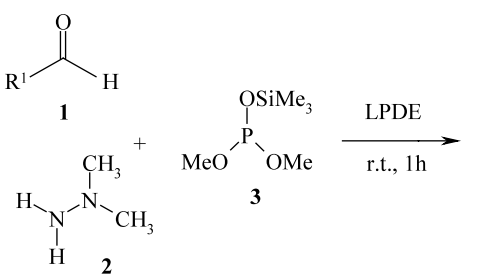
[a]*Chemistry Department, Tarbiat Modarres University, PO Box 14155-4838, Tehran, Iran*
[b]*Chemistry Department, Imam Hossein University, PO Box 16575-347, Tehran, Iran*

Received 27 June 2001; revised 28 August 2001; accepted 7 September 2001

Abstract—Various α-hydrazinophosphonates were prepared on the basis of three-component (aldehydes, *N*,*N*-dimethylhydrazine, and dimethyl(trimethylsilyl)phosphite, coupling reactions via $LiClO_4$-catalyzed tandem reactions. © 2001 Published by Elsevier Science Ltd.

The addition of nucleophiles to C=N bonds is a synthetically important method of preparing many types of nitrogen-containing compounds of biological importance. Among these, α-amino phosphonates are particularly worth mentioning. As an analog of α-aminoalkylphosphonic acids, α-hydrazinoalkylphosphonic acids and their derivatives are of potential biological importance. For example, several of these compounds show a good safety effect against the phytotoxic action of chloroacetanilide herbicides.[1] To the best of our knowledge, only a few examples of the synthesis of α-hydrazinophosphonic acids have been reported: these include the base-catalyzed condensation of diethyl phosphite with aliphatic aldazines followed by subsequent acid hydrolysis[2] (this method, however, was not suitable for aryl aldazines), a selective reduction of the α-hydrazonophosphonic acids with $NaBH_3CN$ or $BH_3{\cdot}THF$,[3] nucleophilic substitution of 1-sulfonyloxyalkylphosphonates by hydrazine,[4] and nucleophilic substitution of 3-methoxy-1,2,3,6-tetrahydropyridazine derivatives by dimethylphosphite in the presence of Lewis acid.[5]

Three-component condensation reactions are interesting and important, not only because two bonds are formed in one-pot, but also because the methodology is useful for making a broad variety of compound libraries. However, it is difficult to extend the Lewis acid-catalyzed three-component condensation to the synthesis of amine derivatives because the strong affinity of many Lewis acids for amino groups does not allow regeneration of the Lewis acids in the reaction.[6] Moreover, the Lewis acids can be decomposed by the amine and water which are present at the stage of amine derivative formation.[7] It has been reported that three-component condensation reactions of aldehydes,



R¹	Yield 4 %
n-ethyl	97
i-propyl	94
n-propyl	95
tert-butyl	92
n-butyl	94
n-pentyl	90
n-hexyl	85
c-hexyl	96

Scheme 1.

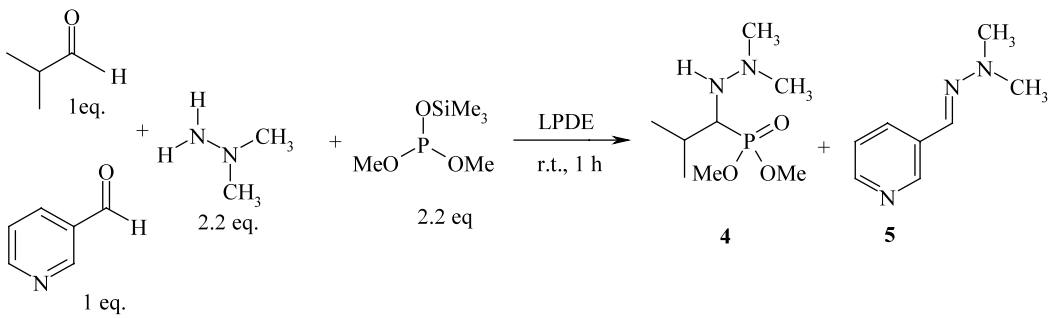
* Corresponding author.

† In memory of Hans Otto Kalinowski.

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)01702-6

amines or phenylhydroxylamine and nucleophiles such as *O*-silylated keteneacetals, trimethylsilylcyanide, dimethylphosphite and dimethyl trimethylsilyl phosphite take place in lithium perchlorate/diethyl ether solution (5.0 M) to yield, β-aminoesters,[8] α-aminonitriles,[9] α-aminophosphonates,[10] α-cyanohydroxylamines[11] and *N*-trimethylsilyloxy-α-aminophosphonates,[12] respectively. Herein, we wish to report that α-hydrazinophosphonates can be prepared in good yields by a new multicomponent synthesis in which a hydrazone (generated in situ from the aldehyde and *N*,*N*-dimethylhydrazine) is reacted with dimethyl trimethylsilyl phosphite as a nucleophile, in lithium perchlorate/diethyl ether (LPDE) solution (5.0 M) at room temperature, within 1 h.[13] It should be noted that a solution of aldehyde the **1**, *N*,*N*-dimethylhydrazine **2** and dimethyl trimethylsilyl phosphite **3** in diethyl ether remains unchanged after 4 h at room temperature. Several examples of the present three component coupling reactions are summarized in Scheme 1.

This method seems to be a good route to α-alkyl hydrazinophosphonates. However, benzaldehyde, *p*-methoxy-benzaldehyde, 3-pyridine carbaldehyde and cinnamaldehyde are inert to nucleophilic addition of dimethyl trimethylsilyl phosphite in the one-pot three-component reaction.[14] Additionally, we found that hydrazonophosphonation of an aliphatic aldehyde rather than an aromatic was performed with more than 99% selectivity. Thus, the reaction of isobutyraldehyde and 3-pyridine carbaldehyde with *N*,*N*-dimethylhydrazine and dimethyl trimethylsilyl phosphite in 5.0 M LPDE solution give α-hydrazinophosphonate **4** and 3-pyridinehydrazone **5**, respectively.



In conclusion, we report a mild and efficient method for preparation of α-hydrazinophosphonate derivatives, that is suitable for a variety of substituted aldehydes. Applications of this methodology to the preparation of enantiomerically enriched α-hydrazinophosphonates and the synthesis of natural products are in progress.

Acknowledgements

Research supported by the National Research Council of I. R. Iran as a National Research project under the number 984.

References

1. Diel, P.; Maier, L. Eur. Pat. Appl. EP 1985, 143078; *Chem. Abstr.* **1985**, *103*, 215544m.
2. (a) Rachon, J.; Wasielewski, C. *Rocz. Chem.* **1976**, *50*, 477; (b) Baraldi, P. G.; Guarneri, M.; Moroder, F.; Pollini, G. P.; Simoni, D. *Synthesis* **1982**, 653.
3. Yuan, C.; Chen, S.; Xie, R.; Feng, H. *Phosphorus, Sulfur, Silicon* **1995**, *106*, 115.
4. Yuan, C.; Li, C. *Synthesis* **1996**, 507.
5. Kaname, M.; Yoshinaga, K.; Arakawa, Y.; Youshifuji, S. *Tetrahedron Lett.* **1999**, *40*, 7993.
6. Niimi, L.; Serita, K-i.; Hiraoka, S.; Yokozawa, T. *Tetrahedron Lett.* **2000**, *41*, 7075.
7. Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039.
8. Heydari, A.; Ipaktschi, J. *Chem. Ber.* **1994**, *127*, 1761.
9. Heydari, A.; Fatemi, P.; Alizadeh, A.-A. *Tetrahedron Lett.* **1998**, *39*, 3049.
10. Heydari, A.; Karimian, A.; Ipaktschi, J. *Tetrahedron Lett.* **1998**, *39*, 5773.
11. Heydari, A.; Larijani, H.; Emami, J.; Karami, B. *Tetrahedron Lett.* **2000**, *41*, 2471.
12. Heydari, A.; Zarei, M.; Alijanianzadeh, R.; Tavakol, H. *Tetrahedron Lett.* **2001**, *42*, 3629.
13. **A typical experimental procedure**: To a mixture of aldehyde (2 mmol) in 5 M LPDE (4 ml) was added *N*,*N*-dimethylhydrazone (2.2 mmol) at room temperature. The mixture was stirred for 5 min and dimethyl trimethylsilyl phosphite (2.2 mmol) was added. The mixture was stirred for 15 min then water was added and the product was extracted with CH_2Cl_2. The organic phase was collected, dried (Na_2SO_4) and evaporated to afford the crude product. The product was purified by flash chromatography (hexan–ethyl acetate). ^1H NMR, ^{13}C NMR, IR and MS spectra were entirely consistent with the assigned structures. Selected data as follows: **4** ($R^1 = i$-propyl): oil ^1H NMR (500 MHz, $CDCl_3$) δ 3.56 (d, $^3J_{P-H} = 7$ Hz, 3H, OCH_3), 3.54 (d, $^3J_{P-H} = 7$ Hz, 3H, OCH_3), 3.1 (bs, 1H, NH), 2.84 (dd, $^2J_{P-H} = 14.6$ Hz, $^2J_{H-H} = 4$ Hz, 1H, H1), 2.24 (s, 6H, NCH_3), 1.95 (m, 1H, H2), 0.86 (d, $^3J_{H-H} =$ 7Hz, 3H, CH_3), 0.81 (d, $^3J_{H-H} = 7$Hz, 3H, CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 59.7 (d, $^2J_{P-C} = 146$ Hz, C1), 51.56 (d, $^3J_{P-C} = 7$ Hz, OCH_3), 50.30 (d, $^3J_{P-C} = 7$ Hz, OCH_3), 46.25 (s, NCH_3), 27.2 (s, CH), 18.77 (d, $^4J_{P-C} =$ 11 Hz, CH_3), 17.11 (d, $^4J_{P-C} = 5$ Hz, CH_3): **4** ($R^1 =$ *tert*-butyl): oil ^1H NMR (90 MHz, $CDCl_3$) δ 3.86 (d, $^3J_{P-H} = 2.7$ Hz, 3H, OCH_3), 3.72 (d, $^3J_{P-H} = 2.7$ Hz, 3H, CH_3), 3.0 (bs, 1H, NH), 2.9 (d, $^2J_{P-H} = 18$ Hz, 1H, H1),

2.50 (s, 6H, NCH_3), 1.2 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 65.39 (d, $^2J_{P-C}=141$ Hz, C1), 52.25 (d, $^3J_{P-C}=7$ Hz, OCH_3), 52.20 (d, $^3J_{P-C}=7$ Hz, OCH_3), 47.50 (s, NCH_3), 34.38 (d, $^3J_{P-C}=3$ Hz, C_2), 27.82 (d, $^4J_{P-C}=6.6$ Hz, CH_3): **4** ($R^1=n$-propyl): oil ^1H NMR (500 MHz, $CDCl_3$): δ 3.67 (d, $^3J_{P-H}=5.5$ Hz, 3H, OCH_3), 3.65 (d, $^3J_{P-H}=5.5$ Hz, 3H, OCH_3), 3.37 (bs, 1H, NH), 2.98 (m, 1H, H1), 2.34 (s, 6H, NCH_3), 1.61–1.34 (m, 4H, CH_2-CH_2), 0.86 (t, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.48 (d, $^2J_{P-C}=153$ Hz, C1), 52.78 (d, $^3J_{P-C}=7$ Hz, 3H, OCH_3), 52.55 (d, $^3J_{P-C}=6.5$ Hz, 3H, OCH_3), 47.79 (s, 6H, NCH_3), 31.31 (s, CH_2), 19.66 (d, $J_{P-C}=9$ Hz, CH_2), 14.0 (s, CH_3); **4** ($R^1=c$-hexyl): oil ^1H NMR (500 MHz, $CDCl_3$): δ 3.71 (d, $^3J_{P-H}=8.8$ Hz, 3H, OCH_3), 3.69 (d, $^3J_{P-H}=8.8$ Hz, 3H, OCH_3), 3.41(bs, 1H, NH), 2.95 (dd, $^2J_{P-H}=14.6$ Hz, $^2J_{H-H}=3.5$ Hz, 1H, H1), 2.37 (s, 6H, NCH_3), 1.76–1.58 (m, 6H), 1.24–1.18 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 61.22 (d, $^2J_{P-C}=146$ Hz, C1), 52.68 (d, $^3J_{P-C}=7$ Hz, OCH_3), 52.47 (d, $^3J_{P-C}=7$ Hz, OCH_3), 47.77 (s, NCH_3), 38.70 (s, CH), 30.67 (d, $J_{P-C}=10$ Hz, CH_2), 28.9 (d, $J_{P-C}=3$ Hz, CH_2), 26.7 (s, CH_2), 26.6 (s, CH_2), 26.3 (s, CH_2).

14. When a solution of aromatic or heteroaromatic aldehyde and *N*,*N*-dimethylhydrazine was treated with dimethyl trimethylsilyl phosphite in LPDE solution (5.0 M) at room temperature for 1 h, the corresponding hydrazone type product was obtained with high yield.