ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 4, pp. 621–623. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © O.V. Tsepaeva, A.V. Nemtarev, V.F. Mironov, 2017, published in Zhurnal Organicheskoi Khimii, 2017, Vol. 53, No. 4, pp. 614–615.

SHORT COMMUNICATIONS

Reaction of Methyl 2-Methylidene-3-oxolup-20(29)-en-28-oate with Triphenylphosphonium Trifluoromethanesulfonate

O. V. Tsepaeva[a], A. V. Nemtarev[a, b],* and V. F. Mironov[a, b]

[a] *Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, ul. Arbuzova 8, Kazan, 420088 Tatarstan, Russia*
**e-mail: a.nemtarev@mail.ru*

[b] *Kazan (Volga Region) Federal University, ul. Kremlevskaya 18, Kazan, 420008 Tatarstan, Russia*

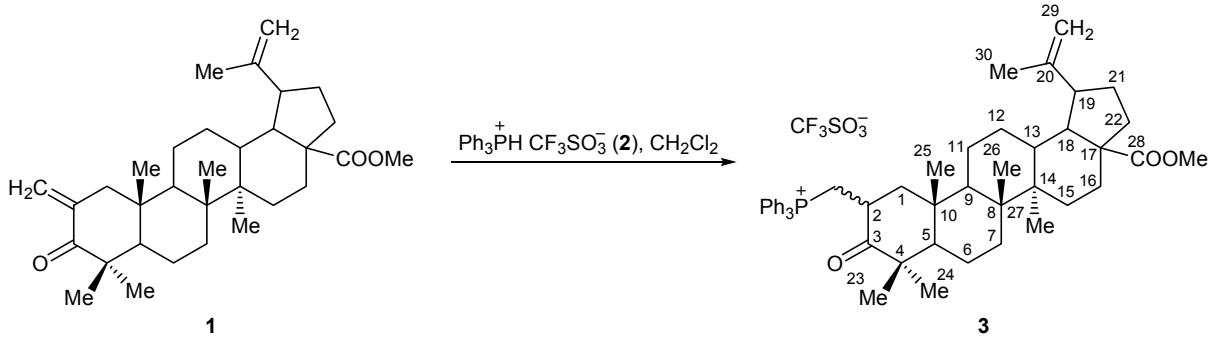
Received January 18, 2017

Abstract—Phosphorylation of methyl 2-methylidene-3-oxolup-20(29)-en-28-oate with triphenylphosphonium trifluoromethanesulfonate in methylene chloride at 20°C afforded 90% of a γ-oxoalkylphosphonium salt containing a terpenoid fragment, [28-methoxy-3,28-dioxolup-20(29)-en-2-ylmethyl]triphenylphosphonium trifluoromethanesulfonate, as a mixture of two epimers (2*S*/2*R*) at a ratio of 2 : 1.

DOI: 10.1134/S1070428017040212

Compounds containing a phosphorus–carbon bond rarely occur in nature and are mainly produced by microorganisms [1–4]; some of them were found to exhibit herbicidal (bialafos, phosphinothricin) and antibiotic activities (fosfomycin, plumbemycin, fosmidomycin) [4, 5]. Introduction of P–C-containing fragments into organic molecules is a popular method used to not only endow target structures with various practically important properties not inherent to their precursors but also facilitate their transport through membranes [6]. This is especially significant for physiologically active natural compounds whose modification is performed most frequently with the simplest three- and four-coordinate phosphorus derivatives such as trialkyl phosphites, dialkyl phosphorochloridites, dialkyl hydrogen phoshites, phosphorous triamides, and phosphates [7]. Phosphates and phosphonates were used to synthesize compounds with a P–C bond in the presence of metal complex catalysts [8]. At present, increased interest is observed in the synthesis of antimicrobial and antitumor agents on the basis of functionally substituted phosphonium salts of such triterpenoids of the lupane series as betulin and betulinic acid [9, 10], in which the lipophilic triarylphosphonium group is responsible for targeted delivery to mitochondria [11]

Herein, we propose a new convenient approach to the introduction of a triphenylphosphonium cation into the molecule of a lupane derivative, methyl 2-methylidene-3-oxolup-20(29)-en-28-oate (**1**) which was synthesized by condensation of formaldehyde with betulonic acid methyl ester in the presence of potassium carbonate [11]. The proposed approach is based on the reaction of **1** with triphenylphosphonium



1 **3**

trifluoromethanesulfonate (**2**) prepared by mixing triphenylphosphine with trifluoromethanesulfonic acid in methylene chloride (δ_P 4.7 ppm, $^1J_{PH}$ = 524 Hz). Reagent **2** added to the exocyclic C^2=C double bond of **1** activated by the neighboring C^3=O carbonyl group. Phosphonium salt **3** was formed as a mixture of epimers. Its $^{31}P–\{^1H\}$ NMR spectrum showed two singlets at δ_P 22.7 and 24.3 ppm with an intensity ratio of 1:2. In the ^1H NMR spectrum of **3** we observed signals of the $C^{29}H_2$ protons as an *AX* spin system in the region δ 4.6–4.7 ppm, which indicated conservation of the lupane skeleton (the latter is unstable in acidic medium). The P^+CH_2 carbon atom resonated in the $^{13}C–\{^1H\}$ NMR spectrum as two doublets at δ_C 23–24 ppm ($^1J_{PC}$ = 52–53 Hz). The C^1 and C^3 signals of epimers of **3** appeared in the $^{13}C–\{^1H\}$ NMR spectrum as doublets at δ_C 48–51 and 214–218 ppm with coupling constants $^3J_{PC}$ of 9.8–11.2 and 2.4–3.2 Hz, respectively. These findings convincingly proved the addition of phosphonium cation to the exocyclic carbon atom of **1** with formation of salt **3**.

Thus, using triphenylphosphonium trifluoromethanesulfonate as an example, we have shown that PH phosphonium salts may be convenient reagents for the introduction of a phosphonium group into terpenoids containing an α,β-unsaturated carbonyl fragment; as a result, γ-oxoalkylphosphonium salts can be obtained under mild conditions.

The ^1H, ^{13}C, $^{13}C–\{^1H\}$, and $^{31}P–\{^1H\}$ NMR spectra were recorded on a Bruker Avance 400 spectrometer using $CDCl_3$ as solvent. The IR spectrum was measured in KBr on a Bruker Tenzor-27 spectrometer with Fourier transform. The mass spectrum was obtained on a Bruker MALDI-TOF Ultraflex III instrument using 2,5-dihydroxybenzoic acid as matrix.

[28-Methoxy-3,28-dioxolup-20(29)-en-2-ylmethyl]triphenylphosphonium trifluoromethanesulfonate (3). A solution of 0.41 g (1 mmol) of salt **2** in 10 mL of methylene chloride was added dropwise with stirring to a solution of 0.48 g (1 mmol) of compound **1** in 20 mL of methylene chloride. The mixture was stirred for 2 h (TLC), the solvent was removed under reduced pressure (12 mm), the residue was washed with petroleum ether and dissolved in 3 mL of ethyl acetate, and the product was precipitated with petroleum ether and filtered off. Yield 0.8 g (90%, diastereoisomer ratio 2:1). IR spectrum, ν, cm^{-1}: 3065, 2951, 2869, 1721 (C=O), 1642, 1589, 1440, 1389, 1378, 1263, 1223, 1155, 1112, 1031, 983, 883. ^1H NMR spectrum, δ, ppm (*J*, Hz): epimer **3a**: 0.33 s, 0.65 s, 0.85 s, 0.85 s, and 0.99 s (15H, $C^{23}H_3$, $C^{24}H_3$, $C^{25}H_3$, $C^{26}H_3$, $C^{27}H_3$); 2.96 m (1H, 19-H), 3.20 m (1H, CH_2P, $^2J_{PH}$ = 12.0–14.0, $^2J_{HH}$ = 12.0–14.0; overlapped by the 2-H signal of **3b**), 3.42 m (1H, 2-H), 1.68 s (3H, $C^{30}H_3$), 3.57 m (1H, CH_2P, $^2J_{HH}$ = 12.0–14.0, $^2J_{PH}$ = 9.2), 3.65 s (3H, OCH_3), 4.59 br.s and 4.71 br.s (1H each, 29-H), 7.64–7.77 m (Ph); epimer **3b**: 0.53 s, 0.88 s, 0.90 s, 0.91 s, and 0.94 s (15H, $C^{23}H_3$, $C^{24}H_3$, $C^{25}H_3$, $C^{26}H_3$, $C^{27}H_3$); 1.66 s (3H, $C^{30}H_3$), 2.96 m (1H, 19-H), 3.20 m (1H, 2-H, overlapped by the CH_2P signal of **3a**), 3.50–3.80 m (2H, CH_2P), 3.66 s (3H, OCH_3), 4.59 br.s and 4.71 br.s (1H each, 29-H), 7.64–7.77 m (Ph). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz) (the multiplicity in the $^{13}C–\{^1H\}$ NMR spectrum is given in parentheses): epimer **3a**: 218.0 br.m (d) (C^3, $^3J_{PH}$ = 2.4), 176.6 br.s (s) (C^{28}), 150.3 br.m (s) (C^{20}), 134.7 d.m (s) (C^p, $^1J_{CH}$ = 164.6), 133.8 d.m (d) (C^o, $^2J_{PC}$ = 9.9, $^1J_{CH}$ = 164.3), 130.0 d.d.d (d) (C^m, $^3J_{PC}$ = 12.8, $^1J_{CH}$ = 165.7, $^2J_{CH}$ = 7.3), 119.2 d.m (d) (C^i, $^1J_{PC}$ = 86.5), 109.7 t.m (s) (C^{29}, $^1J_{CH}$ = 154.7), 38.3 d.d (d) (C^2, $^2J_{PC}$ = 4.4), 23.9 d (PCH_2, $^1J_{PC}$ = 52.8 Hz); epimer **3b**: 214.5 br.m (d) (C^3, $^3J_{PC}$ = 3.2), 176.6 br.s (s) (C^{28}), 150.1 br.m (s) (C^{20}), 134.2 d.m (s) (C^p, $^1J_{CH}$ = 164.6), 132.5 d.m (d) (C^o, $^2J_{PC}$ = 11.3, $^1J_{CH}$ = 164.0), 129.4 d.d.d (d) (C^m, $^3J_{PC}$ = 13.2, $^1J_{CH}$ = 164.6, $^2J_{CH}$ = 7.3), 119.3 d.m (d) (C^i, $^1J_{PC}$ = 86.9), 109.8 t.m (s) (C^{29}, $^1J_{CH}$ = 154.7), 38.8 d.d (C^2, $^2J_{PC}$ = 4.4), 22.6 d (PCH_2, $^1J_{PC}$ = 53.9 Hz). $^{31}P–\{^1H\}$ NMR spectrum, δ_P, ppm: 22.7 (**3a**), 24.3 (**3b**). Mass spectrum: *m*/*z* 743.4 $[M - CF_3SO_3]^+$. Found, %: C 67.93; H 7.14; P 3.04. $C_{51}H_{64}F_3O_6PS$. Calculated, %: C 68.59; H 7.22; P 3.47. *M* 893.09.

This study was performed under financial support by the Russian Foundation for Basic Research, by the Academy of Sciences of Tatarstan Republic (project no. 15-43-02456_r-povolzh'e-a), and by the Russian Government Program of Competitive Growth of Kazan Federal University.

REFERENCES

1. Kittredge, J.S. and Roberts, E., *Science*, 1969, vol. 164, p. 37.
2. Thayer, J.S., *Appl. Organomet. Chem*., 1989, vol. 3, p. 203.
3. Seto, H. and Kuzuyama, T., *Nat. Prod. Rep*., 1999, vol. 16, p. 589.
4. Seweryn, P., Van, L.B., Kjeldgaard, M., Russo, C.J., Passmore, L.A., Hove-Jensen, B., Jochimsen, B., and Brodersen, D.E., *Nature*, 2015, vol. 525, p. 68.

5. Blodgett, J.A.V., Zhang, J.K., Yu, X., and Metcalf, W.W., *J. Antibiot*., 2016, vol. 69, p. 15.
6. Wiemer, A.J. and Wiemer, D.F., *Top. Curr. Chem*., 2014, vol. 360, p. 115.
7. Illy, N., Fache, M., Ménard, R., Negrell, C., Caillol, S., and David, G., *Polymer Chem*., 2015, vol. 6, p. 6257.
8. Beletskaya, I.P. and Kazankova, M.A., *Russ. J. Org. Chem*., 2002, vol. 38, p. 1391.
9. Król, S.K., Kiełbus, M., Rivero-Müller, A., and Stepulak, A., *BioMed. Res. Int*., 2015, vol. 2015, article ID 584189.
10. Csuk, R., Stark, S., Nitsche, C., Barthel, A., and Siewert, B., *Eur. J. Med. Chem*., 2012, vol. 53, p. 337.
11. Ross, M.F., Kelso, G.F., Blaikie, F.H., James, A.M., Cochemé, H.M., Filipovska, A., Da Ros, T., Hurd, T.R., Smith, R.A.J., and Murphy, M.P., *Biochemistry* (Moscow), 2005, vol. 70, p. 222.