Application of N-nitrosoureas in the synthesis of organophosphorus compounds

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N-nitrosoureas which are readily accessible from the reaction of urea derivatives with sodium nitrite and aqueous H_2SO_4 reacted with acetylenic esters in the presence of Ph_3P in ethyl acetate at ambient pressure to give stable phosphorus ylides. This methodology is introduced as a simple and inexpensive procedure for the preparation of organophosphorus compounds in excellent yields.

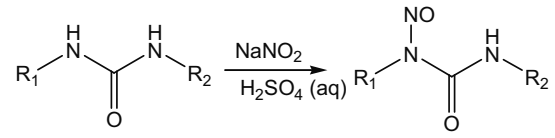
Keywords: phosphorus ylides, N-nitrosourea, acetylenic esters, Wittig reaction

Among the phosphorus compounds, phosphorus ylides play an important role in the synthesis of organic molecules,[1-7] because they give an elegant access to other functionalities and a number of these compounds were employed in the preparation of natural products such as β-carotene.[8] They are usually prepared by deprotonation of the corresponding phosphonium salt.[9,10] Synthesis of a phosphonium salt often requires forcing conditions. Frequently, the phosphine and organic halide must be heated to reflux for several hours, and in some cases days, to obtain the desired phosphonium salt.[11] N-nitrosoureas which were derived from urea can be used for specific applications. N-alkyl N-nitrosoureas present a very promising class of anti-tumor drugs which have become quite common in clinical practice.[12-15]

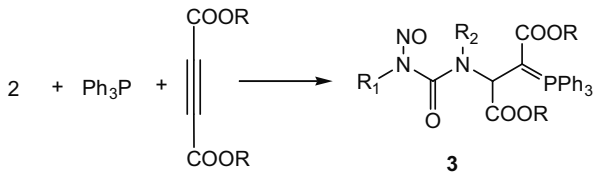
These compounds show high activity and are characterised by a broad spectrum of anti-tumor activity.

Although many impressive ylide and nitroso compound syntheses have been reported, our literature survey reveals that N-nitrosourea derivatives with a chain along with two functional groups such as an ylide moiety and an ester group are unknown. In view of their importance, there is a continuing interest in developing versatile synthetic routes for the preparation of such compounds. We hope to develop a general protocol for the efficient synthesis of N-alkyl-1-nitrosoureas or N, N'-dialkyl-1-nitrosoureas containing these functionalities. Here, we present our progress towards this goal. The present work is based on the reaction of N-alkyl or N,N'-dialkyl N-nitrosoureas with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine.

N-nitrosourea derivatives were readily prepared by treating the N-alkyl urea or N, N-dialkyl urea **1**, with sodium nitrite in the presence of an acid such as aqueous H_2SO_4 (3%). The reaction proceeds with excellent yields to give N-alkyl N-nitrosoureas or N,N-dialkyl N-nitrosoureas **2** respectively. Compounds **3a–e**, were obtained as white powders after mixing of compound **2** and acetylenic esters in the presence of Ph_3P in hexane–ethyl acetate at ambient temperature for about 30 min (Scheme 1).



1 **2**

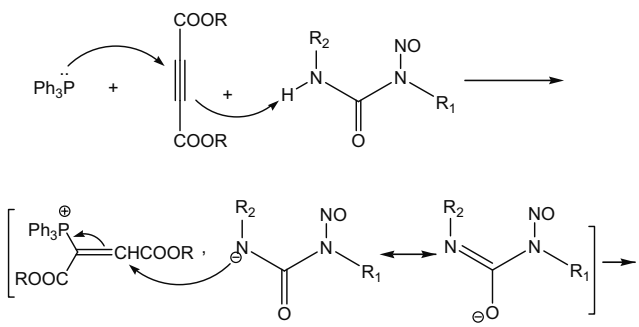


3

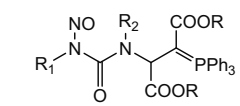
3	R	R_1	R_2	Yield (%)
a	Me	Me	Me	95
b	Et	Me	Me	85
c	Me	Et	H	92
d	Me	Me	H	95
e	Et	Me	H	85

Scheme 1

The formation of **3** can be explained by conversion of the phosphonium salt I to an ylide. The phosphonium salt **I** resulted from the initial addition of Ph_3P to dialkyl acetylenedicarboxylates and concomitant protonation of a 1 : 1 adduct by NH-acid **2**. Then the conjugated base of the NH-acid attacks the positively charged ion to form products **3a–e** (Scheme 2).



I



3

Scheme 2

We proposed a reaction similar to the Wittig reaction could be performed between the phosphorus ylide moiety and an NO group. Thus compounds **3a-e** were subjected to an intramolecular reaction by heating in boiling dioxane (Scheme 3). In all cases, the mentioned compounds seemed too unreactive towards cyclisation for this to be a realistic possibility. It seems most likely that the resonance form II causes the NO group not be able to react with the ylide moiety.

The structures of compounds **3a–e** are assigned based on the IR, ^1H NMR and ^{13}C NMR spectra and elemental CHN-analyses data. The ^1H and ^{13}C NMR spectroscopic data for these compounds exhibit a mixture of two rotational isomers. The ylide moiety of these compounds is strongly conjugated

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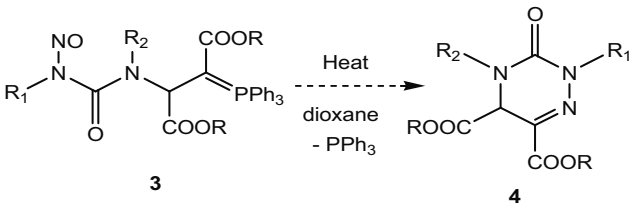
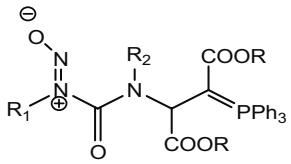


3 4



II

Scheme 3

with the adjacent carbonyl group and rotation about the partial double bond in 3-(*E*) and 3-(*Z*) isomers is low on the NMR time scale at ambient temperature. Rotational isomers in phosphoranes have been previously established and reported in the literature[16,17] (Scheme 4).

The ratio of rotational isomers was determined from the ^{1}H NMR spectrum. As an example, the ^{1}H NMR spectrum of compound **3a** exhibits the mixture of these isomers as 66% and 34% for *Z* and *E* isomers respectively.

The spectrum of compound **3a** shows eight sharp lines (δ 3.03, 3.04, 3.18, 3.26, 3.32, 3.59, 3.81 and 3.85) arising from the methyl groups and the methoxy protons along with signals from the methine protons at δ 4.77 and 4.79 which appear as two doublets ($^3J_{PH}$ = 14.3 and $^3J_{PH}$ = 17.0 Hz) for the major and minor geometrical isomers respectively. In the **3a-(*Z*)** isomer, one methoxy group is appeared at δ 3.03 ppm due to the anisotropy effect of the phenyl groups in Ph_3P. The ^{13}C NMR spectrum of compound **3a** is in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **3b** are similar to those of compound **3a**, except for the signals from the ester groups, which appear as characteristic resonance lines with the corresponding chemical shifts. The ^{1}H and ^{13}C NMR spectra of compounds **3c–e** are in agreement to the proposed structures (see Experimental).

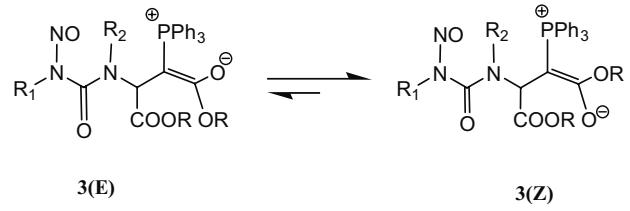
In conclusion, we have employed the nitrosoureas in the synthesis of organophosphorus compounds such as phosphorus ylides by using a three-component condensation. The products containing several functional groups were obtained in excellent yields and this simple procedure can be introduced as a practical method for the preparation of urea derivatives including nitroso and ylide groups.

Experimental

All common reagents and solvents were used as obtained from commercial suppliers without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 AVANCE (^{1}H NMR at 500 MHz, and ^{13}C at 125.77 MHz,). Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Elemental CHN analyses were performed by University of Tarbiat Moalem using a Heracus CHN-ORapid analyser. IR spectra were measured on a Mattson 1000 FT-IR spectrometer.

General procedure

At ambient temperature dimethyl acetylenedicarboxylate (0.24 ml, 2 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.53 g, 2 mmol) and N-nitroso-N,N-dimethyl urea (0.24 g, 2 mmol) in a mixture of hexane–ethyl acetate. After the addition was complete (approximately 30 minutes) the mixture was stirred for an additional 1 h and was subsequently filtered. The solid collected in the filter was washed thoroughly with ethyl acetate to give a white powder.



3(E) 3(Z)

Scheme 4

Dimethyl 2-(methyl{[methyl(nitrosomethyl)amino] carbonyl}amino)-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate (**3a**): (0.98 g, m.p 156–158 °C, yield 95%); IR (KBr) ($\nu_{max,}$ cm^{-1}): 1753, 1706, and 1636 (C=O). Isomer (*Z*) (66%) ^{1}H NMR: δ 3.03 and 3.32 (s, 2 NCH_3), 3.18 and 3.59 (s, 2 OCH_3), 4.77 (d, $^3J_{PH}$ = 17.0 Hz, P =C–CH), 7.46–7.69 (30H, m, arom)*. ^{13}C NMR: δ 29.51 and 34.55 (s, 2NCH_3), 49.16 and 52.49 (2OCH_3), 60.82 (d, $^2J_{PC}$=17.9 Hz P=C-^{13}CH), 126.57 (d, $^1J_{PC}$ = 92.6 Hz, C^{ipso}), 128.86 (d, $^3J_{PC}$ = 12.3 Hz, C^{meta})*, 132.25 (d, $^4J_{PC}$ = 2.1 Hz, C^{para})*, 134.9 (d, $^2J_{PC}$ = 9.9 Hz, C^{ortho}), 154.91 (C=O)*, 169.77 (d, $^2J_{PC}$ = 11.4 Hz, C=O), 171.94 (d, $^3J_{PC}$ = 17.1 Hz, C=O)*. Isomer (*E*) (34%), ^{1}H NMR: δ 3.04 and 3.26 (s, 2 NCH_3), 3.81 and 3.85 (s, 2 OCH_3), 4.79 (d, $^3J_{PH}$ = 14.3 Hz, P =C–^{13}CH). ^{13}C NMR: δ 29.51 and 33.98 (s, 2 NCH_3), 50.21 and 52.22 (2OCH_3), 60.35 (d, $^2J_{PC}$=18.0 Hz P=C–^{13}CH), 125.93 (d, $^1J_{PC}$=91.7 Hz, C^{ipso}), 133.58 (d, $^2J_{PC}$ = 11.5 Hz, C^{ortho}), 170.43 (d, $^2J_{PC}$ = 17.1 Hz, C=O). Anal. Calcd for $C_{27}H_{28}N_3O_6P$ (521.51): C, 62.18; H, 5.41; N, 8.06%. Found: C, 61.95; H, 5.48; N, 7.92%.

Diethyl 2-(methyl{[methyl(nitrosomethyl)amino] carbonyl}amino)-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate (**3b**): (0.94 g, m.p 139–141 °C, yield 85%); IR (KBr) ($\nu_{max,}$ cm^{-1}): 1760, 1716, and 1636 (C=O). Isomer (*Z*) (67%) ^{1}H NMR: δ 0.48 (t, $^3J_{HH}$ = 6.95 Hz, CH_3), 1.35 (t, $^3J_{HH}$ = 6.95 Hz, 2 CH_3)*, 3.02 and 3.32 (s, 2 NCH_3), 3.68–4.35 (m, 8H, 4 OCH_2)*, 4.75 (d, $^3J_{PH}$ = 17.8 Hz, P =C–^{13}CH)*, 7.43–7.71 (30H, m, arom)*. ^{13}C NMR: δ 13.97 and 14.29 (s, 2 CH_3), 29.54 and 34.48 (s, 2 NCH_3), 39.26 (d, $^1J_{PC}$ = 126.9 Hz, C = P)*, 60.85 (d, $^2J_{PC}$ = 16.5 Hz, P =C–^{13}CH)*. 61.01 and 61.09 (2 OCH_2), 126.79 (d, $^1J_{PC}$ = 91.6 Hz, C^{ipso}), 128.76 (d, $^3J_{PC}$ = 12.1 Hz, C^{meta}), 132.18 (s, C^{para})*, 133.56 (d, $^2J_{PC}$ = 9.8 Hz, C^{ortho})*, 154.83 (C=O)*, 169.31 (d, $^2J_{PC}$ = 10.9 Hz, C=O), 171.26 (d, $^3J_{PC}$ = 11.2 Hz, C=O)*. Isomer (*E*) (33%), ^{1}H NMR: δ 1.19 (t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.04 and 3.29 (s, 2 NCH_3). ^{13}C NMR: δ 14.19 and 14.78 (s, 2 CH_3), 29.53 and 34.04 (s, 2 NCH_3), 57.81 and 58.53 (2 OCH_2), 60.36 (d, $^2J_{PC}$ = 11.6 Hz, P =C–^{13}CH), 126.18 (d, $^1J_{PC}$ = 91.3 Hz, C^{ipso}), 128.81 (d, $^3J_{PC}$ = 12.0 Hz, C^{meta}), 170.22 (d, $^2J_{PC}$ = 17.5 Hz, C=O). Anal. Calcd for $C_{29}H_{32}N_3O_6P$ (549.57): C, 63.38; H, 5.87; N, 7.65%. Found: C, 63.40; H, 5.79; N, 7.62%.

Dimethyl 2-(ethyl{[(nitrosomethyl)amino]carbonyl}amino)-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate (**3c**): (0.96 g, m.p 119–121 °C, yield 92%); IR (KBr) ($\nu_{max,}$ cm^{-1}): 1743, 1719, and 1636 (C=O). Isomer (*Z*) (57%) ^{1}H NMR: δ 0.99 (t, $^3J_{HH}$ = 6.9 Hz, CH_3), 3.16 and 3.75 (s, 2 OCH_3), 3.80 (q, $^3J_{HH}$ = 7.4 Hz, NCH_2), 4.63 (dd, $^3J_{PH}$ = 15.0 Hz, P =C–CH, $^3J_{HH}$ = 8.8 Hz), 7.52–7.76 (30H, m, arom)*, 8. 53 (d, $^3J_{HH}$ = 8.8 Hz, NH). ^{13}C NMR: δ 12.12 (2 CH_3)*, 34.55 (NCH_2), 42.51 (d, $^1J_{PC}$ = 112.8, P=C), 49.11 and 52.41 (2 OCH_3), 53.69 (d, $^2J_{PC}$ = 17.6 Hz, P =C–^{13}CH), 126.67 (d, $^1J_{PC}$ = 92.7 Hz, C^{ipso}), 128.71 (d, $^3J_{PC}$ = 11.7 Hz, C^{meta}), 132.19 (d, $^4J_{PC}$ = 2.6 Hz, C^{para})*, 133.80 (d, $^2J_{PC}$ = 9.8 Hz, C^{ortho})*, 152.57 (C=O), 170.14 (d, $^2J_{PC}$ = 15.3 Hz, C=O)*, 173.26 (d, $^3J_{PC}$ = 7.3 Hz, C=O). Isomer (*E*) (43%), ^{1}H NMR: δ 1.00 (t, $^3J_{HH}$ = 6.7 Hz, CH_3), 3.58 and 3.73 (s, 2 OCH_3), 3.83 (q, $^3J_{HH}$ = 7.0 Hz, CH_2), 4.66 (dd, $^3J_{PH}$ = 16.2 Hz, P =C–CH, $^3J_{HH}$ = 8.6 Hz), 8. 02 (d, $^3J_{HH}$ = 8.6 Hz, NH). ^{13}C NMR: δ 34.62 (NCH_2), 43.61 (d, $^1J_{PC}$ = 113.2, P =C), 50.17 and 52.39 (2 OCH_3), 52.95 (d, $^2J_{PC}$ = 16.8 Hz, P =C–^{13}CH), 126.0 (d, $^1J_{PC}$ = 92.1 Hz, C^{ipso}), 128.81 (d, $^3J_{PC}$ = 8.7 Hz, C^{meta}), 152.19 (C=O), 173.20 (d, $^3J_{PC}$ = 7.7 Hz, C=O). Anal. Calcd for $C_{27}H_{28}N_3O_6P$ (521.51): C, 62.18; H, 5.41; N, 8.06%. Found: C, 62.42; H, 5.36; N, 7.81%.

Dimethyl 2-(methyl{[(nitrosomethyl)amino]carbonyl}amino)-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate (**3d**): (0.96 g, m.p 154–156 °C, yield 95%); IR (KBr) ($\nu_{max,}$ cm^{-1}): 1765, 1716, and 1641 (C=O). Isomer (*Z*) (60%) ^{1}H NMR: δ 3.11 (s, NCH_3), 3.15 and 3.73 (s, 2 OCH_3), 4.60 (dd, $^3J_{PH}$ = 15.6 Hz, P =C–CH, $^3J_{HH}$ = 8.7 Hz), 7.51–7.73 (30H, m, arom)*, 8. 6 (1H, d, $^3J_{HH}$ = 8.3 Hz, NH). ^{13}C NMR: δ 26.56 (NCH_3)*, 41.70 (d, $^1J_{PC}$ = 128.5, P =C)*, 49.11 and 52.41 (2 OCH_3), 53.70 (d, $^2J_{PC}$ = 17.3 Hz P =C–^{13}CH), 126.6 (d, $^1J_{PC}$ = 92.9 Hz, C^{ipso}), 128.71 (d, $^3J_{PC}$ = 11.6 Hz, C^{meta})*, 132.19 (d, $^4J_{PC}$ = 2.9 Hz, C^{para})*, 133.77 (d, $^2J_{PC}$ = 9.9 Hz, C^{ortho})*, 152.69 (C=O), 170.14 (d, $^2J_{PC}$ = 14.7 Hz, C=O)*, 173.23 (d, $^3J_{PC}$ = 13.6 Hz, C=O).

Isomer (*E*) (40%), ^{1}H NMR: δ 3.13 (s, NCH_3), 3.56 and 3.70 (s, 2 OCH_3), 4.64 (dd, $^{3}J_{PH}$ = 17.9 Hz, P =C–CH, $^{3}J_{HH}$ = 9.1 Hz), 8.06 (d, $^{3}J_{HH}$ = 9.1 Hz, NH). ^{13}C NMR: δ 50.17 and 52.39 (2 OCH_3), 52.97 (d, $^{2}J_{PC}$ = 17.9 Hz, P =C–^{13}CH), 125.98 (d, $^{1}J_{PC}$ = 94 Hz, C^{ipso}). Anal. Calcd for $C_{26}H_{26}N_3O_6P$ (507.47): C, 61.54; H, 5.16; N, 8.28%. Found: C, 61.52; H, 5.07; N, 8.24%.

Diethyl 2-(methyl{[(nitrosomethyl)amino]carbonyl}amino)-3-(1,1,1-triphenyl-λ^5-phosphanylidene) succinate (**3e**): (0.91 g, m.p 157–159 °C, yield 85%); IR (KBr) (ν_{max}, cm^{-1}): 1765, 1741, 1690 and 1641 (C=O). Isomer (*Z*) (57%), ^{1}H NMR: δ 0.46 (t, 3JHH = 7.0 Hz, CH_3), 1.23 (t, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 3.11 (s, NCH_3), 3.66–4.24 (8H, m, 4 OCH_2), 4.56 (dd, $^{3}J_{PH}$ = 15.2 Hz, P =C–CH, $^{3}J_{HH}$ = 6.2 Hz), 7.49–7.75 (30H, m, arom)*, 8.62 (d,$^{3}J_{PH}$ = 6.2 Hz, NH). ^{13}C NMR: δ 13.87 and 14.17 (2 CH_3), 26.51 (NCH_3), 42.13 (d, $^{1}J_{PC}$ = 129.8 Hz, P =C), 53.69 (d, $^{2}J_{PC}$ = 17.4 Hz, P =C–^{13}CH), 57.67 and 61.24 (2 OCH_2), 126.80 (d, $^{1}J_{PC}$ = 92.8 Hz, C^{ipso}), 128.61 (d, $^{3}J_{PC}$ = 12.3 Hz, C^{meta}), 132.13 (d, $^{4}J_{PC}$ = 2.6 Hz, C^{para})*, 133.83 (d, $^{2}J_{PC}$ = 9.8 Hz, C^{ortho})*, 152.73 (C=O), 169.69 (d, $^{2}J_{PC}$ = 13.7 Hz, C=O)*, 172.57 (d, $^{3}J_{PC}$ = 8.2 Hz, C=O). Isomer (*E*) (43%), ^{1}H NMR: δ 1.17 (t, $^{3}J_{HH}$ = 7.0 Hz, CH_3), 1.26 (t, $^{3}J_{HH}$ = 7.0 Hz, CH_3), 3.12 (s, NCH_3), 4.58 (dd, $^{3}J_{PH}$ = 15.2 Hz, P =C–CH, $^{3}J_{HH}$ = 7.5 Hz), 8.20 (d,$^{3}J_{HH}$ = 7.5 Hz, NH). ^{13}C NMR: δ 14.17 and 14.85 (2 CH_3), 43.39 (d, $^{1}J_{PC}$ = 137.1 Hz, P =C), 52.98 (d, $^{2}J_{PC}$ = 18.3 Hz P =C–^{13}CH), 58.33 and 61.24 (2 OCH_2), 126.12 (d, $^{1}J_{PC}$ = 88.5 Hz, C^{ipso}), 128.71 (d, $^{3}J_{PC}$ = 12.4 Hz, C^{meta}), 152.36(C=O). Anal. Calcd for $C_{28}H_{30}N_3O_6P$ (535.53): C, 62.80; H, 5.65; N, 7.85%. Found: C, 62.74; H, 5.64; N, 7.78%.

*For two rotamers

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