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A NEW ADDITION REACTION OF TRIALKYL PHOSPHITE AND ALKYL HALIDE TO NITRONE

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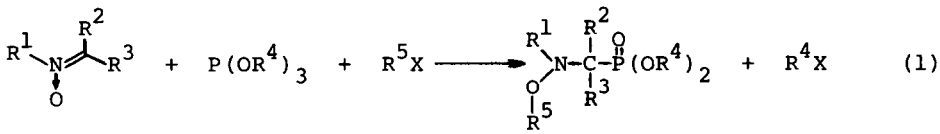
Abstract: N-Substituted 1-(alkoxyamino)alkylphosphonates were obtained by a new addition reaction of trialkyl phosphite and alkyl halide to nitrone. A push-pull type mechanism was suggested for the addition reaction.

Nitrones have attracted many chemists because of their versatile reactivities.[1] And the synthetic utility of nitrone has been widely recognized especially in their 1,3-dipolar addition reactions.[2] Addition reactions of some nucleophiles to the charge-locarized structure of nitrone were also reported.[3] However, to our knowledge, there is no report on the simultaneous addition reaction of electrophile and nucleophile to nitrone.

Herein, we report a new addition reaction of trialkyl phosphite 2 and alkyl halide 3 to nitrone 1 , where one end of nitrone attacks alkyl halide (electrophile) and the other is attacked by phosphite (nucleophile) to yield an N-substituted 1-(alkoxyamino)alkylphosphonate 4. (eq. 1)



(1)

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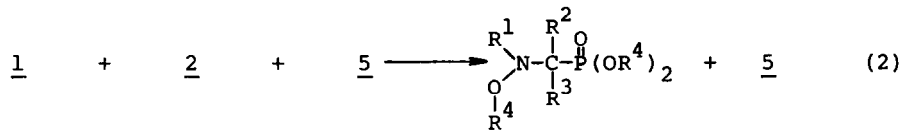


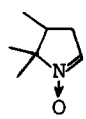
(2)

6

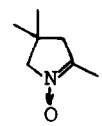
A typical example of the reaction is as follows: A mixture of 4,5,5-trimethyl-Δ^1-pyrroline N-oxide (508 mg, 4 mmol), trimethyl phosphite (496 mg, 4 mmol) and iodomethane (2.84 g, 20 mmol) in an anhydrous benzene (5 ml) was stirred and heated at 40°C under nitrogen. The reaction was monitored by VPC. After 3 hours, the cooled reaction mixture was subjected to column chromatography (silica gel, n-C_6H_{14}-EtOAc gradient) to give O,O-dimethyl 1-methoxy-4,5,5-trimethyl-pyrrolidin-2-ylphosphonate (713 mg,

71%) as an oil. Other reactions were conducted in a similar way. Detailed conditions and the results were listed in Table 1.[4]

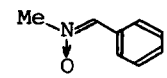
In this reaction, three kinds of reactants were placed and heated all together. A push-pull mechanism was suggested by two blank experiments, where no reaction was observed in the absence of one of the reactants, electrophile (alkyl halide) or nucleophile (phosphite). Salt formation was not detected in each blank reaction, so the stepwise mechanism was excluded. In addition, normal Arbusov products, $R^5P(=O)(OR^4)_2$ and $R^4P(=O)(OR^4)_2$, were not formed appreciablly despite of the presence of excess amounts of alkyl halide. As a matter of fact, catalytic amount of alkyl halide was sufficient for the reaction (entry 7, Table 1), but excess amounts of alkyl halide were used for acceleration of the reaction and improvement of the ratio of 4 : 6 (eqs. 1 and 2). For, the reaction product R^4X also reacted as a second alkyl halide, and by-product 6 was formed in the case where R^4 and R^5 were different (eq. 2). Nucleophilic halogen ion reacted more smoothly ($I > Br >> Cl$) (entries 9, 10, 11, Table 1), and the reaction was accelerated in a polar solvent ($CH_3CN > THF > C_6H_6$) (entries 2, 3, 4, Table 1). These features of the reaction might imply the fact that dealkylation step was essential in completing the reaction as in the case of normal Arbusov reaction.[5]



1a



1b



1c

This reaction was applicable not only to cyclic nitrones, 1a and 1b, but also to acyclic one, 1c. It seemed that the former was more reactive than the latter (entries 1 and 14, Table 1). The difference of reactivity might be due to the inherent instability of distorted five membered ring system. Even the hindered cyclic nitrone, 1b, reacted smoothly to give the corresponding N-substituted 1-alkoxyamino-tert-alkylphosphonate in a good yield (entry 13, Table 1). In addition, diethyl phenylphosphonite reacted easily with 1a and 1b in a similar manner, yielding a diastereomeric mixture of the corresponding O-ethyl alkylphenylphosphinate in good yields (entries 16 and 17, Table 1).

We are now under active investigation on the application of this addition reaction to the syntheses of biologically active compounds.

Table 1. Addition Reaction of Trialkyl Phosphite and Alkyl Halide to Nitrone[a]

entry	reactants 1	2	3	solv.	temp. (°C)	time (hr)	conv.[b] (%)	yield(%)[c] in 4+6 (4/6 ratio)
1	1a	$P(OMe)_3$	MeI	C_6H_6	40	3	100	71
2	1a	$P(OEt)_3$	MeI	C_6H_6	40	5	93	n.d.[d] (99/1)
3	1a	$P(OEt)_3$	MeI	CH_3CN	40	0.5	99	n.d.[d] (88/12)
4	1a	$P(OEt)_3$	MeI	THF	40	3	97	61 (99/1)
5	1a	$P(OMe)_3$	EtI	C_6H_6	70	2	100	74 (91/9)
6	1a	$P(OEt)_3$	EtI	CH_3CN	70	1	100	65
7[e]	1a	$P(OEt)_3$	EtI	CH_3CN	70	1	80	n.d.[d]
8	1a	$P(OMe)_3$	i-PrI	CH_3CN	70	1	100	86 (75/25)
9	1a	$P(OMe)_3$	allyl-I	THF	40	1	100	72 (97/3)
10	1a	$P(OMe)_3$	allyl-Br	THF	40	3	100	56 (95/5)
11	1a	$P(OMe)_3$	allyl-Cl	THF	40	3	0	0
12	1a	$P(OMe)_3$	propargyl-Br	CH_3CN	70	0.5	100	61 (85/15)
13	1b	$P(OMe)_3$	MeI	CH_3CN	40	1	100	78
14	1c	$P(OMe)_3$	MeI	CH_3CN	40	5	23	83
15	1c	$P(OEt)_3$	EtI	CH_3CN	70	5	83	76
16	1a	$PhP(OEt)_2$	EtI	CH_3CN	70	4	100	67[f]
17	1b	$PhP(OEt)_2$	EtI	CH_3CN	70	2	100	71[f]

a) All reactions were carried out with a molar ratio of 1:1:5 (1/2/3), unless otherwise stated. For the general procedures and the structures of reactants and products, 1, 4 and 6, see the text. b) Conversion, based on VPC area intensities. c) Isolated yields, based on conversion. The ratio of 4/6 was calculated from VPC area intensites of the isolated mixture. Each component was separated by preparative VPC and characterized by its spectral (NMR, IR and mass) and analytical data. d) Isolated yield was not determined. e) A molar ratio of 1:1:0.1 (1/2/3) was employed. f) Obtained as a diastereomeric mixture

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4. All compounds showed spectral and analytical data consistent with their structures. Salient spectral data for new compounds follow: O,O-Dimethyl 1-methoxy-4,5,5-trimethylpyrrolidin-2-ylphosphonate (entry 1, Table 1) n_D(25.0°C) 1.4506; IR (neat film) 2875 (s), 1690 (ms), 1455 (m), 1240 (s), 1040 (s), 825 (ms); NMR δ (CCl_4) 0.81 (3H, s), 1.14 (3H, s), 0.80-2.10 (6H, m), 2.95-3.50 (1H, m), 3.63 (3H, s), 3.72 (3H, d, J=10 Hz), 3.78 (3H, d, J=10 Hz); mass spectrum, m/z (relative intensity) 251 (M^+, 0.5), 204 (0.7), 178 (0.6), 172 (1.7), 168 (0.6), 142 (100), 95 (16). O,O-Diethyl 1-(N-ethoxy-N-methylamino)benzylphosphonate (entry 15, Table 1) n_D(25.4°C) 1.4705; IR (neat film) 3030 (w), 2980 (s), 1710 (m), 1600 (w), 1445 (mw), 1390 (m), 1255 (s), 1040 (s), 970 (s), 695 (m); NMR δ (CCl_4) 0.98 (3H, t, J=14 Hz), 1.10 (3H, t, J=14 Hz), 1.33 (3H, t, J=14 Hz), 2.50 (3H, s), 3.30-4.40 (7H, m), 7.10-7.65 (5H, m); mass spectrum, m/z (relative intensity) 301 (M^+, 0), 164 (100), 136 (14), 118 (21), 77 (9).

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