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MITSUNOBU N^3-ALKYLATION OF 1,3,4-OXADIAZOL-2(3*H*)-ONES

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Abstract: The Mitsunobu reaction of 1,3,4-oxadiazol-2(3H)-ones with alcohols leads to N^3-alkylated products in high yields.

In connection with an on-going medicinal chemistry program we required a method which would allow a clean N-alkylation of 1,3,4-oxadiazol-2(3*H*)-ones under neutral conditions. Although oxadiazolones of this type are frequently alkylated by alkyl halides in good yield using base catalysis,[1] we believed that these conditions would be inappropriate for alkylation with secondary halides, and inconsistent with sensitive functionality and conservation of stereochemical integrity in the case of chiral substrates.

The Mitsunobu reaction has been widely applied to the alkylation of heteroatom functions.[2,3] Less information is available on the possibilities for application of this method for the alkylation of heterocycles.[4] Recently, Mitsunobu alkylations of 2-pyridones[5] and 3-methyl-1-phenyl-2-pyrazolin-5-ones[6] were reported to give predominantely O-alkylation. 1,3,4-Oxadiazol-2(3*H*)-ones, like 2-pyridones and pyrazolones, are potentially ambident nucleophiles. Indeed O-alkylation may be conducted under appropriate conditions.[7]

We reasoned that 1,3,4-oxadiazol-2(3*H*)-ones would undergo Mitsunobu alkylation on the basis of a measured[8,9] pK_a of 7.06 for the N^3-H proton, and that the α-effect would contribute to favor N^3-alkylation over O-alkylation.

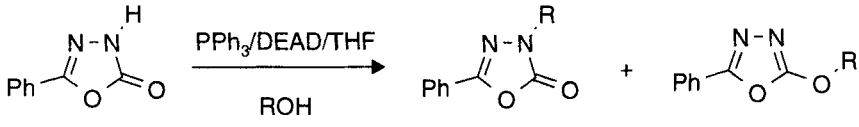
Results and Discussion

The results of this study are shown in the table. The reaction was conducted with commercially available 5-phenyl-1,3,4-oxadiazol-2(3*H*)-one under normal Mitsunobu conditions (triphenyl phosphine/diethylazodicarboxylate in tetrahydrofuran) and with a range of alcohols.

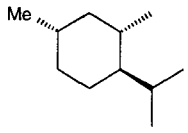
In almost all examples a high yielding N-alkylation was observed. Only in the case of menthol was partial O-alkylation observed. The reaction is applicable to primary, secondary, benzylic and allylic systems. In the case of tertiary butanol only a poor yield of alkylated materiel was recovered. Alkylation of (+)-menthol afforded mainly the N-alkylated *cis*-product (2g).The results of an X-ray diffraction study are in agreement with this structure.[10] Therefore, as expected from the mechanism, clean S_N2 inversion has taken place at the reaction centre.

In conclusion Mitsunobu alkylation is a synthetically useful and convenient method for selective N^3-alkylation of 1,3,4-oxadiazol-2(3*H*)-ones.

Table - Mitsunobu Alkylation of 5-Phenyl-1,3,4-oxadiazol-2(3*H*)-one with alcohols



1 2 3

Example	R	Yield(%)	
		2	3
a	Et	95	-
b	Bn	65	-
c	PhEt	86	-
d	Cyclopentyl	78	-
e	Allyl	84	-
f	t-Bu	18	-
g		76	10

Experimental

^{1}H and ^{13}C NMR spectra were measured at 200 Mhz and 50 Mhz respectively on a Bruker DP200 spectrometer using $CDCl_3$ as the internal standard. Melting points were determined on a Koeffler hot-stage or a Totoli apparatus and are uncorrected. Yields were not optimised.

General procedure for the preparation of compounds 2a-g. In a typical experiment 0.26g (1.5 mmol) of diethylazodicarboxylate was added slowly to a stirred solution of 0.162 (1 mmol) of 5-phenyl-1,3,4-oxadiazol-2(3*H*)-one, (1 mmol) of alcohol and 0.39g (1.5mmol) of triphenylphosphine in 5ml of tetrahydrofuran at 0-4°C under argon. The mixture was stirred at room temperature for one hour and then the solvent removed *in vacuo* and the residue chromatographed on silica gel eluting with a mixture of heptane/ethyl acetate 20/80.

3-Ethyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2a) Yield 95%, Mpt. 46-48° C (lit.[11] yield 26%, Mpt. 46-47°C) ^{1}H-NMR ($CDCl_3$) δ 1.45(t,3H), 3.85(q,2H), 7.4-7.55(m,3H), 7.8-7.9(m,2H); ^{13}C NMR δ13.5, 41.1, 125.6, 128.9, 131.4, 163.3. (Found: C,63.07,63.05; N,14.64,14.62; H,5.31,5.30. Calc. for $C_{10}H_{10}N_2O_2$: C,63.15; N,14.73; H,5.30.

3-Benzyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2b) Yield 65%, Mpt.118-120°C (lit.[12] yield 85%, Mpt.118-119°C) ^{1}H NMR ($CDCl_3$) δ 4.95(s,2H), 7.3-7.55(m,8H), 7.8-7.9(m,2H). Found: C,70.94,70.90; N,10.77,10.87; H,4.86,4.86. Calc. for $C_{15}H_{12}N_2O_2$: C,71.27; N,11.08; H,4.81.

3-(2-Phenylethyl)-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2c) Yield 86%, Mpt. 83-85°C, ^{1}H NMR ($CDCl_3$) δ 3.15(t,2H), 4.05(t,2H), 7.15-7.35(m,5H), 7.4-7.55(m,3H), 7.8-7.95(m,2H). Found: C,71.80,71.92; N,10.37,10.40; H,5.20,5.24. Calc. for $C_{16}H_{14}N_2O_2$: C,72.17; N,10.52; H,5.30.

3-Cyclopentyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2d) Yield 78%, Mpt. 89°C dec., ^{1}H NMR ($CDCl_3$) δ 1.6-1.8(m,2H), 1.85-2.15(m,6H), 4.45-4.65(m,1H),7.4-7.55(m,3H), 7.8-7.95(m,2H). Found: C,67.52,67.57; N,12.02,12.03; H,6.05,6.09. Calc. for $C_{13}H_{14}N_2O_2$: C,67.81; N,12.17; H,6.13.

3-Allyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2e) Yield 84%, Mpt. 54-56°C (lit. yield 85%, Mpt. 58-59°C) ^{1}H NMR ($CDCl_3$) δ 4.5(dd,2H), 5.3-5.55(m,2H), 5.8-6.05(m,1H), 7.45-7.6(m,3H), 7.8-7.95(m,2H). Found: C,65.15,65.10; N,13.63,13.52; H,4.92,4.89. Calc. for $C_{11}H_{10}N_2O_2$: C,65.34; N,13.85; H,4.98.

3-t-Butyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2f) Yield 18%, Mpt. 29-31°C, ^{1}H NMR ($CDCl_3$) δ 1.6(s,9H), 7.4-7.55(m,3H), 7.75-7.9(m,2H). Found: C,66.59,66.51; N,12.35,12.40; H,6.74,6.70. Calc. for $C_{12}H_{14}N_2O_2$: C,66.04; N,12.84; H,6.46.

3-((1S,2S,5R)-Menthyl)-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2g) Yield 76%, Mpt. 45-47°C, $[\alpha]_D$ -3.6° (c=1, MeOH), ^{1}H NMR ($CDCl_3$) δ 0.80-1.05(m,10H), 1.2-1.5(m,3H), 1.7-2.1(m,4H), 4.5-4.6(m,1H), 7.45-7.55(m,3H), 7.8-7.9(m,2H). Found: C,72.16,72.11; N,9.41,9.43; H,8.10,8.10. Calc. for $C_{18}H_{24}N_2O_2$: C,71.97; N,9.33; H,8.05.

2-((1S,2S,5R)-Menthyloxy)-5-phenyl-1,3,4-oxadiazole (3g) Yield 10% ^{1}H NMR ($CDCl_3$) δ 0.80-1.1 (m,10H), 1.1-1.3(m,3H), 1.4-1.9(m,3H), 2.4(br.d,1H), 5.4(s,1H), 7.45-7.55(m,3H), 7.9-8.0(m,2H). M^+ Found: 301, Calc. for $C_{18}H_{24}N_2O_2$: 301.

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