

SOME ASPECTS OF THE MITSUNOBU REACTION

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ABSTRACT

A ^{31}P NMR based study of the Mitsunobu esterification reaction has been undertaken. Three intermediates have been identified: an alkoxytriphenylphosphonium carboxylate, a dialkoxytriphenylphosphorane and an (acyloxy)alkoxytriphenylphosphorane. These three species are in equilibrium with each other, the position of the various equilibria depending on the polarity of the solvent, pKa of the acid and structure of the alcohol. Given the choice between a primary and secondary alcohol, only the phosphorane and oxyphosphonium salt corresponding to the primary alcohol are observed. The implications of these findings for the regioselectivity and stereoselectivity of the Mitsunobu reaction are discussed. Formation of the phosphonium salt is facilitated in more polar solvents or with acids of low pKa. The chemical shift of the alkoxyphosphonium carboxylate was found to be extraordinarily sensitive to the presence of proton sources and solvent, varying over a range of more than 100 ppm. The peripatetic nature of this species has been interpreted in terms of a rapid equilibrium between the alkoxytriphenylphosphonium carboxylate and the corresponding (acyloxy)alkoxytriphenylphosphorane.

Substitution of triphenylphosphine by tributylphosphine using otherwise standard Mitsunobu protocol revealed clean formation of a single intermediate, the alkoxyphosphonium carboxylate. In the absence of acid, at least two species were observed, a dialkoxyphosphorane and an alkoxyphosphonium alkoxide salt.

Replacement of triphenylphosphine by 9-phenyl-9-phosphafluorene confirmed that betaine formation was irreversible and proceeded *via* a nucleophilic addition, not a cheletropic mechanism. Modification of triphenylphosphine by incorporation of an alcoholic or acidic moiety into the structure allowed detection of a possible O,N-phosphorane, an intermediate previously postulated in the Mitsunobu reaction. The synthesis of a series of bulky phosphines showed that steric congestion about the phosphorus atom retarded the rate of betaine (and particularly) phosphorane formation.

An EPR based study has revealed for the first time that radicals are formed during the reaction of phosphines with azodicarboxylates. Evidence is presented to suggest that the betaine arising from this reaction may be formed *via* a single electron transfer pathway.

The reaction of diphenylphosphine and of diphenylphosphine oxide with azodicarboxylates is examined. Diphenylphosphine reacts surprisingly sluggishly, whereas diphenylphosphine oxide reacts rapidly to give the expected addition product.

An 'abnormal' Mitsunobu-like reaction involving catalytic amounts of triphenylphosphine in the presence of diisopropyl azodicarboxylate and α,ω -dithiols to afford disulfides has been studied. The mechanism is discussed in terms of expulsion of

triphenylphosphine from either an S,S-dithiophosphorane or thiophosphonium thiolate salt. The substitution of α,ω -dithiols by α,ω -mercaptoalcohols was also briefly examined.

Finally, diphenyl(2-pyridyl)phosphine was used in place of triphenylphosphine for those Mitsunobu reactions where removal of triphenylphosphine oxide is difficult or troublesome.

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ABBREVIATIONS

The following abbreviations have been used:

A	EPR hyperfine coupling constant
Ar	aryl
Bn	benzyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
δ_C	^{13}C NMR chemical shift
δ_H	^1H NMR chemical shift
δ_P	^{31}P NMR chemical shift
EPR	electron paramagnetic resonance
Et	ethyl
eq.	equivalent
HFS	hyperfine splitting
H ₂ DIAD	diisopropyl hydrazine-1,2-dicarboxylate
IR	infra-red
J	NMR coupling constant
Me	methyl
MeCN	acetonitrile
mp	melting point
NBA	nitrobenzoic acid
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
Pr	propyl
Py	pyridyl
pyr	pyridinium
R	alkyl
R'	alkyl
SET	single electron transfer

TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	tetramethyl silane
TPP	triphenyl phosphine
W _{0.5}	peak width at half height

unless otherwise stated, the following abbreviations refer to multiplicities in NMR spectroscopy:

s	singlet
d	doublet
t	triplet
m	multiplet