Tetrahedron Letters No. 52, pp 5153 - 5156.

0040-4039/78/1222-5153$02.00/0

A MILD QUANTITATIVE METHOD FOR THE SYNTHESIS OF A VARIETY OF HETEROCYCLIC SYSTEMS

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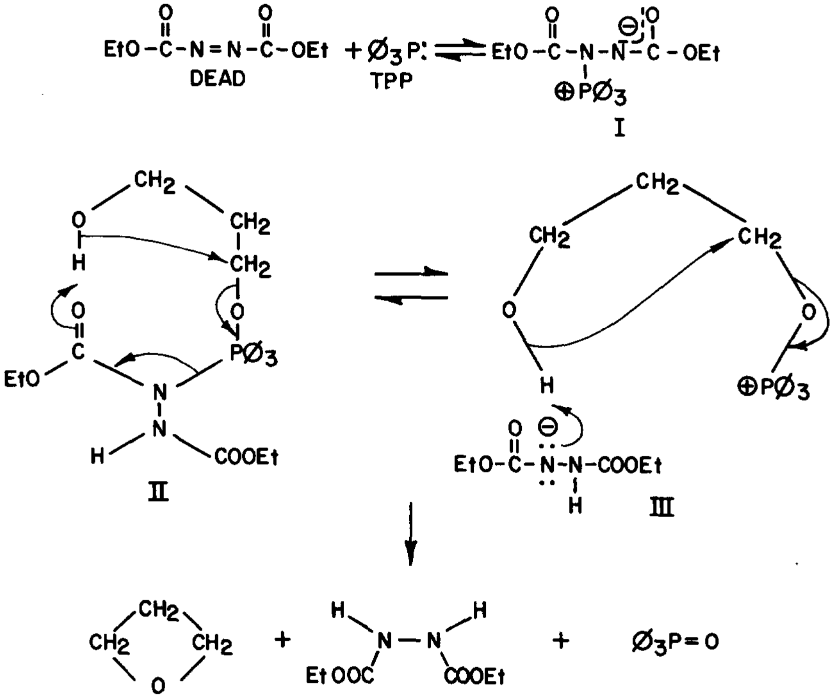
Although a variety of pathways exist for the synthesis of small ring heterocycles,[1] most of these methods are not general for large ring systems and require either strongly basic or acidic media limiting their synthetic utility. Furthermore, many of these reactions are multi-step syntheses whose overall yields are often less than quantitative.[1]

It has been known for a number of years that "oxidative-reductive" dehydrative coupling of certain compounds can occur in the presence of a mixture of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD).[2-11] These reagents have been utilized in the synthesis of nitriles,[2] carbodiimides,[3] ketenimines,[4] isonitriles,[5] O-(N-phenylcarbamyl)hydroxamates,[6] sterol esters,[7] lactones,[8] carbamates[9] via isocyanate intermediates, amines[10] and benzoylated diols.[11] Recently this procedure has been employed for the formation of aryl-alkyl ethers.[12] However, the use of a mixture of DEAD-TPP to form quantitative yields of oxiranes, oxetanes, tetrahydrofurans, tetrahydropyrans, dioxanes, oxepanes and aziridines has *not* been reported. We now wish to announce a quantitative one-step synthesis applicable to a variety of these heterocyclic systems.

The following synthesis of oxetane is representative of the overall synthetic procedure: To a cooled solution of 1.14 gm (0.015 mol) of anhydrous 1,3-propanediol and 3.93 gm (0.015 mol) of triphenylphosphine (TPP) in 30 ml of anhydrous $CDCl_3$ was added dropwise with stirring 3.48 gm (0.02 mol) of diethyl azodicarboxylate (DEAD) under an atmosphere of dry argon. The reaction instantly turned colorless. ^{13}CMR, ^{1}HMR and GLC/MS analyses of the reaction mixture indicated a quantitative conversion of 1,3-propanediol to oxetane.

SCHEME I



This procedure may be extended to the formation of heterocyclic compounds other than oxetane. Cyclic polyethers can be prepared from diol-ethers employing the DEAD-TPP procedure Contacting 2,2'-oxydiethanol (1.06 gm, 0.010 mol) with a solution of TPP (2.62 gm, 0.010 mol) and DEAD (2.61 gm, 0.015 mol) at 25°C in 20 ml of anhydrous tetraline resulted in the formation of 1,4-dioxane in 96-98% yield.

This reaction appears to proceed through the phosphine azo intermediate I previously described by Morrison.[13] The betaine interacts with the diol forming either adduct II or its corresponding salt III[9] (see Scheme I). Collapse of these intermediates generates the cyclic ether, triphenylphosphine oxide and dicarbethoxyhydrazine.

The use of the mixture DEAD-TPP is essential to this synthetic scheme. When a control reaction was carried out without the azo compound, moderate quantities of olefinic material were produced. This last observation supports the findings of Appel and Wihler[14] who reported that secondary alcohols dehydrate to alkenes in 65-74% yield by contacting the alcohol with triphenylphosphine at reflux temperatures.

Table I offers a representative class of compounds that have been converted into heterocycles using this procedure.

Table I

REPRESENTATIVE SYNTHESES OF A VARIETY OF RING SYSTEMS (3,4,5,6 AND 7-MEMBERED) FROM THE CORRESPONDING DIOL OR AMINO-ALCOHOL

STARTING MATERIAL							
Compound	mmol	mmol DEAD	mmol TPP	Reaction Solvent[a]	Reaction Temp. (°C)	Product[b]	%[c] Yield
1,2-propanediol	3.0	4.5	4.5	Toluene	0	2-methyloxirane	100
2,3-butanediol [racemic]	3.0	4.5	4.5	THF	21	2,3-dimethyloxirane	100
Styrene glycol	3.0	4.5	4.5	$CDCl_3$	21	1-phenyloxirane	100
trans-1,2-cyclohexanediol	3.0	4.5	4.5	THF	20	cyclohexylepoxide	100
1,3-propanediol	15.0	20.0	15.0	$CDCl_3$	5	oxetane	98
1,4-butanediol	10.0	15.0	10.0	Tetralin	5	THF	100
1,5-pentanediol	15.0	20.0	15.0	$CDCl_3$	5	tetrahydropyran	95
2,2'-oxydiethanol	10.0	15.0	10.0	Tetralin	25	1,4-dioxane	96
1,6-hexanediol	15.0	20.0	15.0	$CDCl_3$	5	oxepane	94
2-amino-2-methyl-1-propanol	10.0	15.0	15.0	Tetralin	20	2,2-dimethylaziridine	100

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[a] Solvents were of an anhydrous grade and were used without further purification. Reactions were carried out in flame-dried glassware under an atmosphere of dry argon.

[b] Products were identified by high resolution GLC-MS, ^{13}CMR and ^{1}HMR of the reaction mixtures with comparison against authentic samples.

[c] The product yields were determined by GLC with standardization against authentic samples.

Acknowledgements: We thank CONOCO for the use of their research facilities.

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(Received in USA 25 September 1978)