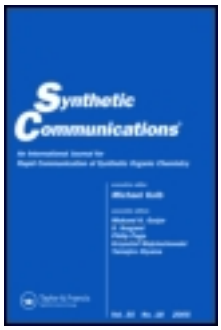

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Propanephosphonic Acid Anhydride-Mediated Cyclodehydration of Maleic Acid Monoamides

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PROPANEPHOSPHONIC ACID ANHYDRIDE-MEDIATED CYCLODEHYDRATION OF MALEIC ACID MONOAMIDES

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Abstract

Propanephosphonic acid anhydride (T3P) has been proposed as a novel reagent for the preparation of maleic acid isoimides from the corresponding monoamides. A series of substituted aromatic and aliphatic isoimides have been prepared in good yield. The main advantage of this synthetic method is the use of environmentally benign, cost-efficient reagents and solvents, which are also safer to handle than the ones employed previously.

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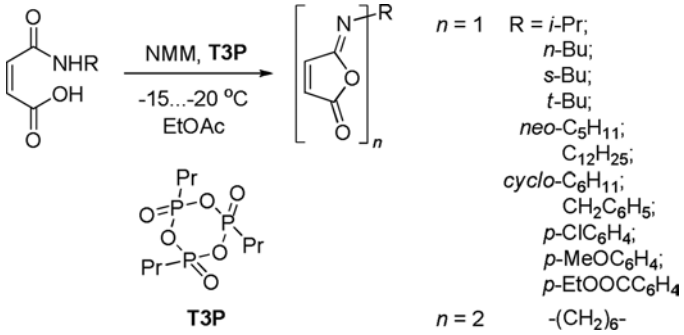

INTRODUCTION

Propanephosphonic acid anhydride (T3P, Figure 1) has been recently used for a wide variety of dehydration reactions. Its use for large scale processes has been extensively promoted by scientists at several pharmaceutical companies, as it is considered a cost-efficient and environmentally benign reagent.[1,2]

T3P has been employed for the synthesis of amides from carboxylic acids[1,3,4] as well as for dehydration of amides to yield nitriles.[5] Several heterocyclic compounds have also been prepared in T3P-mediated reactions.[7-9] In many reactions a new carbon – nitrogen bond has been formed, or bond order has been increased.[7]Our aim was to explore the possibilities of expanding the use of this versatile reagent, so as to include cyclodehydration of maleic acid monoamides (**1**). This reaction may proceed to yield either the thermodynamically preferred maleic acid imides or the somewhat labile isoimides.[10] While both compounds are of great interest in organic chemistry, the higher reactivity of maleic acid isoimides (**2**) makes them especially appealing as reactive intermediates in many synthetic sequences that lead to polyamides,[11]polymerizable surfactants,[12,13] and □-lactams,[14] to name just a few (Scheme 1).

The reagents currently used for the synthesis of isoimides **2** are cyclohexylcarbodiimide[15,16] and ethyl chloroformate,[16] and they both are highly undesirable because of serious safety concerns. In recognition of this problem, some other reagents have been suggested recently, including cyanuric chloride[17] and 2-chloro-1,3-dimethylimidazolinium chloride.[18] However, probably because of somewhat limited utility of these reagents for other similar transformations, their advantages in cyclodehydration of monoamides **1** have not been widely recognized.

T3P could in this case be an excellent alternative, as it is already widely employed in organic synthesis, it is user-friendly and in dehydration reactions produces only innocuous by-products.[1]The reagentused to prepare isoimides **2** has to be able to effect dehydration of monoamides **1** at temperatures low enough to suppress thermal isomerization of isoimides to imides, and the reaction medium must be devoid of chemical species able to promote catalytic isomerization. We proposed that T3P corresponds to these two requirements: it is an efficient and gentle dehydrating reagent.

RESULTS AND DISCUSSION

The requisite monoamides **1** were prepared by simple acylation of the corresponding amines with maleic anhydride.[19] As our aim was to determine the scope and applicability of T3P-mediated cyclodehydration of monoamides **1**, we decided to explore this reaction for structurally different monoamides **1**: substituted aromatic, simple aliphatic, as well as □- and □-branched aliphatic (Scheme 2, Table 1).

We initially carried out dehydration of monoamides **1** under conditions described earlier to work well for other T3P-mediated reactions. T3P is usually available as a solution in different solvents. Previously isoimides **2** have almost invariably been synthesized in dichloromethane solution,[15,20] and even up to date it still remains the solvent of choice.[17,18] As we wished to develop an environmentally benign synthetic method for the preparation of isoimides **2**, we replaced dichloromethane with ethyl acetate. Two equivalents of a tertiary amine have to be used in most reactions employing T3P, presumably to convert the carboxylic acid group in the substratesto the more nucleophilic carboxylate anion and to prevent the reaction medium from becoming acidic, as propanephosphonic acid is liberated in the course of reaction. *N*-Methylmorpholine(NMM) has been suggested as a good choice.[21] It has already been noted that the tertiary amine has to be added before T3P to avoid possible side reactions.[5] We observed that this order of addition also helped to achieve homogeneous reaction medium, as several monoamides **1** were poorly soluble in ethyl acetate. In a few cases when a clear solution could not be obtained, it turned out to be advantageous to reflux the solution for a few minutes before addition of T3P, so as to ensure that monoamides **1** were completely converted to the corresponding NMM salts. The solution of T3P was added at -15…-20°C, and the reaction was left to proceed at +4°C. Under these conditions the reaction was complete over night, the only exceptionbeing preparation of *bis*-isoimide **2l** that went to completion only at room temperature. As usual for T3P-mediated reactions, reaction by-products could be successfully removed by extraction with water.[22] Even though isoimides **2** are rather susceptible to hydrolysis,[23] extraction with water to remove reaction by-products did not present a significant

problem in this case. Further purification of the obtained isoimides **2** was achieved by dissolution in dry diethyl ether and removal of the unreacted monoamides by filtration. Crystallization or chromatographic purification were not required, and indeed were better avoided to prevent isomerization of isoimidesto imides.

The yields of isoimides **2** were generally high and in the same range as obtained by both the classical and the recently developed methods(Table 1). A lower yield was obtained for *tert*-butyl isoimide **2d**, yet it can be readily accounted for by unfavorable sterical interaction during the reaction. The lowest reactivity was exhibited by *bis*-monoamide **2l**, as has already been observed with other dehydrating reagents. A detailed comparison with the recently introduced methods is not possible, since 2-chloro-1,3-dimethylimidazolinium chloride has been used for the synthesis of only threeisoimides,[18] while cyanuric chloride has been used mainly for the synthesis of aromatic isoimides.[17]

In conclusion, we have developed a novel method for the preparation of isoimides **2** that is similar to published methods in terms of yield, but is clearly advantageous from the environmental point of view. We have also broadened the applicability of T3P–a newly introduced dehydrating reagent, and validated that this reagent combines efficiency and gentleness, necessary to convert monoamides **1** into isoimides **2**.

EXPERIMENTAL

All reagents and solvents were purchased from *Merck* and used as received. T3P was also obtained from *Merck* as a 50% solution in ethyl acetate. Monoamides **1** were prepared as described before.[19] NMR spectra were recorded on a *Varian* 400 MHz instrument. Chemical shifts are referenced to the NMR solvent. IR spectra were obtained using a *Perkin Elmer Frontier* spectrometer. Elemental analysis was performed using a *PerkinElmer2400Series* II instrument.

General Procedure For The Synthesis Of Maleic Acid Isoimides (2)

Maleic acid monoamide **1**(1.70 mmol or 0.85 mmol*bis*-monoamide **1l**) was dissolved or suspended in dry ethyl acetate and NMM(0.37 mL, 3.4 mmol) was added. In case the monoamide did not dissolve completely, the solution was heated 1-2 min to reflux. The solution was cooled to -15…-20°C, and a 10% solution of T3P in ethyl acetate (5.4 g of solution, 1.7 mmol) was added dropwise with stirring over 10 min. With continued stirring, the solution was allowed to reach +4°C over 1 h and was left at this temperature over night (cyclodehydration of *bis*-monoamide **1l** was effected at room temperature). The solution was extracted twice with water (2×15 mL) and once with brine (15 mL). The organic layer was collected, dried with 4 Å molecular sieves and concentrated*invacuo* at room temperature. The residue was taken up in dry diethyl ether (40 mL), filtered and concentrated again to yield pure isoimide **2**.

SUPPORTING INFORMATION

Analytical data, including full previously unreported spectroscopic data for isoimides **2a**, **2g** and **2l**, and ^{1}H and ^{13}C NMR spectra of isoimides **2a**, **2g, 2l** and **2k** (the only new

compound) can be found via the "Supplementary Content" section of this article's Webpage.

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1,2,4-oxadiazoles, 1,3,4-oxadiazoles, and 1,3,4-thiadiazoles. *Tetrahedron* **2009**, *65*, 9989–9996.

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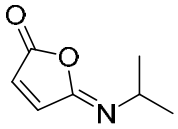
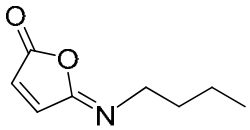
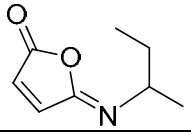
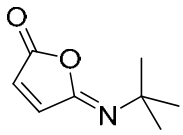
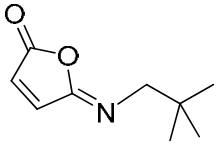
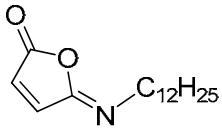
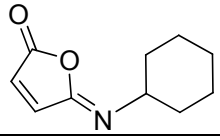
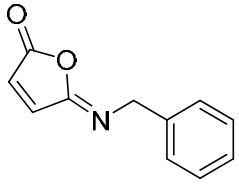
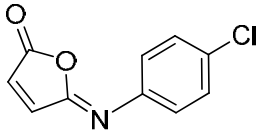
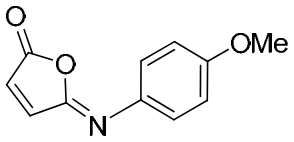
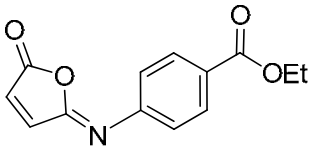
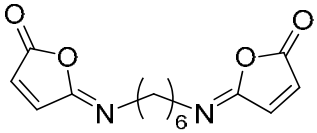
Table 1. Synthesis of maleic acid isoimides **2** using T3P and other reagents

Entry	Product	2	Yield (%)		Mp (°C)	
			T3P	Lit.	Found	Lit.
1		**2a**	80%	[a] 74[24]	oil	
2		**2b**	85%	[a] 77[24] [a] 60[23] [a] 52[16] [c] 79[16]	oil	
3		**2c**	88%	[a] 85[23]	oil	

4		**2d**	51%	[a] 97[23] [a] 82[20]	30-32	30-32.5[23]
5		**2e**	81%	[a] 87[23]	50.0-51.7	45-46.5[23]
6		**2f**	75%	[a] 87[23] [c] 88[23]	42.1-43.8	42-44[23]
7		**2g**	85%	[c] 72[20] [d] 53[18]	37.2-38.8	36-38[20]
8		**2h**	70%	[a] 91[23] [a] 40[20] [c] 79[23]	49.0-50.0	49.5-50[23] oil[20]
9		**2i**	85%	[b] 93[17] [a] 90[25] [a] 85[23] [c] 98[23]	94.6-96.5	100-103[17] 96-98[25] 96-97[23]
10		**2j**	96%	[a] 72[23] [a] 60[26] [b] 91[17]	74.0-75.9	77-79[23] 75[26] 75[17]
11		**2k**	93%		59.8-61.4	
12		**2l**	51%	[a] 65[20] [a] 52[16]	93.0-94.5	95-96[2] 94-96[16]

Dehydrating agent used:

[a] Dicyclohexylcarbodiimide

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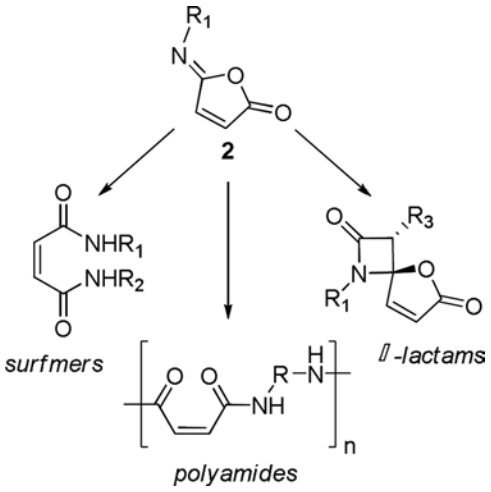
[b] Cyanuric chloride/triethylamine

[c] Ethylchloroformate/triethylamine

[d] 2-Chloro-1,3-dimethylimidazolinium chloride/triethylamine

Scheme 1. Synthetic utility of maleic acid isoimides **2**



Scheme 2. Synthesis of isoimides **2**

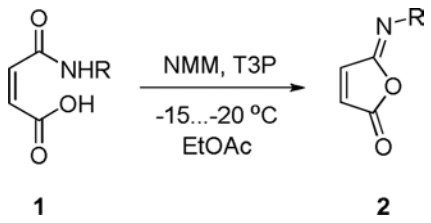


Fig. 1. Propanephosphonic acid anhydride (T3P)