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Convenient propylphosphonic anhydride (T3P®)-mediated synthesis of β-sultams

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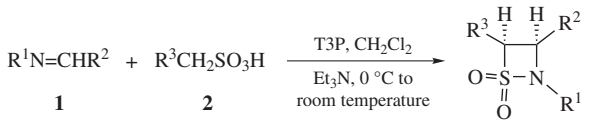
[2+2] Cycloaddition of imines with sulfenes (prepared *in situ* from alkanesulfonic acids under the action of propylphosphonic anhydride T3P) afforded the corresponding *cis* β-sultams.

Propylphosphonic anhydride (T3P®) is a green coupling reagent and water scavenger. During the processing it usually forms a water soluble salt which is readily removed upon the aqueous work up.[1] This reagent was used in the one-pot synthesis of several organic compounds from carboxylic acids,[2] Beckmann rearrangement,[3] Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones[4] and Fischer-type indolization.[5]

β-Sultams (1,2-thiazetidine-1,1-dioxides) are regarded as sulfonyl analogues of β-lactam antibiotics as well as cyclic derivatives of taurine (2-aminoethanesulfonic acid). The reactivity of β-sultams is usually higher than that of the analogous β-lactam systems (~10^3-fold)[6] and acyclic sulfonamides (at least 10^7-fold).[7] β-Sultams have shown some biological activities such as inhibitors of elastases[8,9] and D,D-peptidase[10] and anti-inflammatory agents.[11] Furthermore, they were utilized as various synthetic equivalents as well as building blocks for the construction of other heterocycles.[12]

A number of methods has been reported for the synthesis of β-sultams[13] among which the [2+2] cycloaddition of sulfenes and imines was most widely used.[14] Generally, sulfonyl chlorides served as precursor of sulfenes, however, sulfonyl chlorides are highly corrosive and hygroscopic. Yadav and coworkers used alkoxymethylene-*N*,*N*-dimethyliminium salts[15] in the synthesis of β-sultams from imines and sulfonic acids.[16]

Herein, the efficiency of the T3P in the one-pot synthesis of β-sultams from imines and sulfonic acids under simple, green and mild conditions is reported.



Scheme 1

Table 1 Reaction conditions in the synthesis of β-sultam **3a** ($R^1 = R^3 = Ph$, $R^2 = 4\text{-}ClC_6H_4$).

Entry	Solvent	*T*/°C	T3P/equiv.	Yield (%)
1	DMF	25	1.0	55
2	THF	25	1.0	36
3	CH_2Cl_2	25	1.0	71
4	Toluene	25	1.0	43
5	CH_2Cl_2	25	1.5	79
6	CH_2Cl_2	0	1.5	91
7	CH_2Cl_2	–15	1.5	85
8	CH_2Cl_2	0	1.3	76

α-Toluenesulfonic acid **2a** was selected as a source of sulfenes to optimize the reaction conditions (see Scheme 1, $R^1 = R^3 = Ph$, $R^2 = 4\text{-}ClC_6H_4$, Table 1). At first the reaction of Schiff base **1a** (1 equiv.) and sulfonic acid **2a** (1 equiv.) in the presence of T3P (1 equiv., 50% solution in DMF) and Et_3N (5 equiv.) in dry DMF at room temperature was conducted. As expected, *cis* β-sultam **3a** was obtained in 55% yield. Indication of stereochemistry of β-sultam **3a** was deduced from the coupling constants of H-3 and H-4 which were calculated to be $J = 8.6$ Hz for the *cis* stereoisomer that is favourably compared with those reported previously.[12(b),14(d)] After this successful result, effect of solvent, temperature and amount of the reagent were screened (Table 1).

As it is shown in Table 1, dichloromethane is the best solvent among the solvents tested. When the reaction was started at 0 °C or –15 °C and then was continued overnight at room temperature, the yield of **3a** increased perhaps due to low stability of sulfenes (entries 6, 7). It was found that 1.5 equiv. of the T3P was needed to provide the complete consumption of imine **1a** and the highest yield of product **3a**.

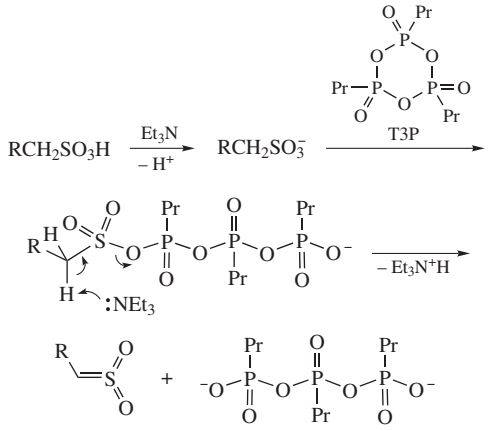
Next, other β-sultams **3b–l** were synthesized by treatment of 1.0 mmol of imines with 1.5 mmol of alkanesulfonic acids and 1.5 mmol of T3P in the presence of triethylamine in dry dichloromethane at 0 °C (Scheme 1, Table 2). Then the reaction mixtures were stirred overnight at room temperature.

The β-sultams **3a–l** were obtained with complete *cis*-selectivity by a mild and simple processing, whereas the secondary products were removed by a simple aqueous work-up. The purification of β-sultams was performed by short column chromatography on silica gel (EtOAc–hexane, 3 : 7) and all products were characterized using their spectral data and elemental analyses.†

Table 2 Synthesis of β-sultams **3a–l** with the use of the reagent T3P.

Entry	R^1	R^2	R^3	Product	Yield (%)
1	Ph	$4\text{-}ClC_6H_4$	Ph	**3a**	91
2	$4\text{-}MeOC_6H_4$	$4\text{-}O_2NC_6H_4$	Ph	**3b**	90
3	$4\text{-}EtOC_6H_4$	$4\text{-}ClC_6H_4$	Ph	**3c**	93
4	Cyclohexyl	$4\text{-}MeC_6H_4$	Ph	**3d**	91
5	Cyclohexyl	$4\text{-}ClC_6H_4$	Ph	**3e**	89
6	$PhCH_2$	Ph	Ph	**3f**	92
7	Me	$4\text{-}O_2NC_6H_4$	Ph	**3g**	83
8	Me	$4\text{-}MeOC_6H_4$	Ph	**3h**	87
9	$4\text{-}MeOC_6H_4$	$4\text{-}O_2NC_6H_4$	Me	**3i**	71
10	Cyclohexyl	$4\text{-}ClC_6H_4$	Me	**3j**	68
11	Cyclohexyl	$4\text{-}MeC_6H_4$	Me	**3k**	74
12	Cyclohexyl	Ph	Et	**3l**	78

The data in Table 2 show that the yields were somewhat lower when ethanesulfonic acid or propanesulfonic acid were used (entries 9–12). This may be due to lower stability of alkyl sulfenes in comparison with that of corresponding aryl sulfenes. The plausible mechanism of sulfene formation from alkanesulfonic acids and T3P is outlined in Scheme 2.



Scheme 2

† *General procedure for the synthesis of β-sultams* **3a–l**. The T3P (1.5 mmol, 50% solution in DMF) was added to a solution of sulfonic acid (1.5 mmol), imine (1 mmol) and triethylamine (5.0 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C and the mixture was stirred overnight at room temperature. The reaction mixture was washed successively with saturated $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed to give the crude product, which was purified by short column chromatography on silica gel (EtOAc–hexane, 3 : 7) to give pure β-sultams **3a–l**. Spectral data for known compounds **3b** and **3d–l** have been previously reported.

3-(4-Chlorophenyl)-2,4-diphenyl-1,2-thiazetidine-1,1-dioxide **3a**: white solid, mp 175–177 °C. IR (KBr, ν/cm^{-1}): 1123, 1303 (SO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.68 (d, 1H, H-4, *J* 8.8 Hz), 4.85 (d, 1H, H-3, *J* 8.8 Hz), 6.83–7.96 (m, 14H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.1 (C-3), 56.9 (C-4), 114.8, 116.0, 118.4, 124.5, 126.2, 127.9, 129.5, 130.2, 138.6, 140.7, 146.2, 152.5 (aromatic carbons). Found (%): C, 65.08; H, 4.47; N, 3.85; S, 8.74. Calc. for $C_{20}H_{16}ClNO_2S$ (%): C, 64.95; H, 4.36; N, 3.79; S, 8.67.

3-(4-Chlorophenyl)-2-(4-ethoxyphenyl)-4-phenyl-1,2-thiazetidine-1,1-dioxide **3c**: white solid, mp 180–182 °C. IR (KBr, ν/cm^{-1}): 1137, 1315 (SO_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.38 (t, 3H, Me, *J* 7.0 Hz), 3.94 (q, 2H, OCH_2, *J* 7.0 Hz), 4.57 (d, 1H, H-4, *J* 8.5 Hz), 4.81 (d, 1H, H-3, *J* 8.5 Hz), 6.82–8.03 (m, 13H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.1 (Me), 62.6 (OCH_2), 55.0 (C-4), 57.2 (C-3), 112.8, 115.2, 119.7, 121.1, 127.3, 128.6, 129.0, 133.6, 137.2, 143.5, 146.1, 155.4 (aromatic carbons). Found (%): C, 63.95; H, 5.02; N, 3.31; S, 7.83. Calc. for $C_{22}H_{20}ClNO_3S$ (%): C, 63.84; H, 4.87; N, 3.38; S, 7.75.

In summary, T3P has been proven to be an excellent reagent to access β-sultams from imines and sulfonic acids in a one-pot synthesis under mild conditions, which may promote wider use of these valuable compounds.

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