Mitsunobu-like Processes with a Novel Triphenylphosphine–Cyclic Sulfamide Betaine

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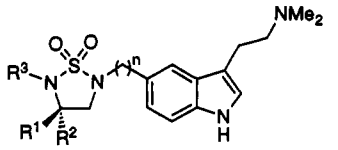
Summary: An unprecedented adduct **10** between triphenylphosphine (TPP) and 3,3-dimethyl-1,2,5-thiadiazolidine 1,1-dioxide (**8**) is described, which can be regarded as a stable source of the $[Ph_3P]^+$ species, and was utilized to efficiently promote the coupling between alcohols and carboxylic or nitrogen acids in a Mitsunobu-like manner.

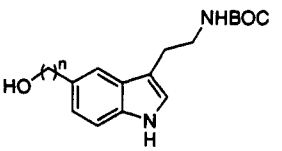
As part of a research program in our laboratories directed toward the identification of novel molecular entities for the treatment of migraine,[1] a synthesis of tryptamines **1–4** (Chart 1) and related analogues was required. Because of literature precedent for the alkylation of imidocarbonates,[2] sulfonamides,[3] and phthalimides,[4] one of the approaches developed involved the coupling of alcohols **5** and **6** with the appropriate cyclic sulfamides **7** and **8**, utilizing a Mitsunobu reaction.[5] While this methodology was applicable to **7** and closely related analogues (e.g., $R^1 = R^2 = H$, R^3 = Et, ^{i}Pr, Bn), the reaction unexpectedly followed a completely different pathway in the case of the *gem*-dimethyl derivative **8**. The characterization and potential utilities of the novel triphenylphosphine (TPP)–cyclic sulfamide adduct **10**, which was isolated from these latter attempted couplings, together with some new insights into the mechanism of the Mitsunobu reaction, are the subject of the present paper.[6]

Under the standard Mitsunobu conditions (DEAD added to a solution of the alcohol, TPP, and the cyclic sulfamide in THF at rt) alcohols **5** and **6** failed to yield the expected alkylated products when reacted with **8**.[1b] In both cases, formation of copious amounts of a white solid was evident after about half of the addition of DEAD, and on workup after several hours at rt, the alcohols were recovered in 53–88% yields.[7] Analysis of the isolated white solid by TLC (silica gel, Et_2O) showed it to be a mixture of triphenylphosphine oxide (TPPO) and **8**. In view of the propensity of TPPO to form highly crystalline hydrogen-bond donor–acceptor complexes[8] with a variety of organic molecules, the structure of the adduct was at first thought to be **9**. However, attempted preparation of

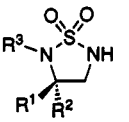
Chart 1



1, $R^1 = R^2 = H$, $R^3 = Me$, n = 1
2, $R^1 = R^2 = H$, $R^3 = Me$, n = 2
3, $R^1 = R^2 = Me$, $R^3 = H$, n = 1
4, $R^1 = R^2 = Me$, $R^3 = H$, n = 2

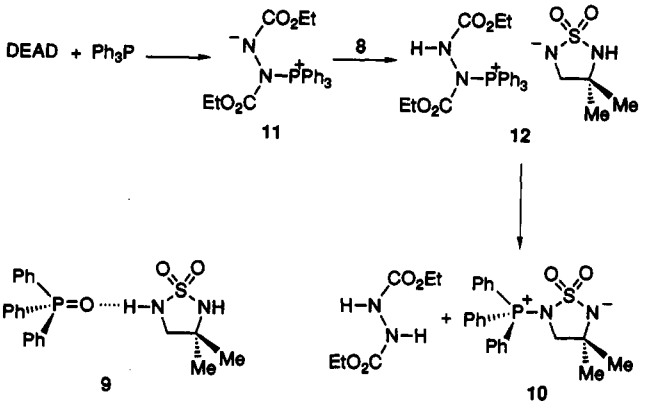


5, n = 1
6, n = 2



7, $R^1 = R^2 = H$, $R^3 = Me$
8, $R^1 = R^2 = Me$, $R^3 = H$

Scheme 1



9 by mixing TPPO and **8** in THF failed. Additionally, the ^{31}P-NMR analysis of the solid in DMSO-d_6 which showed a single resonance at δ +27.96 ppm (H_3PO_4 as external reference), together with traces of a minor singlet unequivocally assigned to TPPO (δ +19.63 ppm), ruled out hydrogen-bonded complex **9** as the possible structure.

Suitable crystals of the solid were grown from a CH_2Cl_2–MeCN mixture,[9] and a single-crystal X-ray analysis was performed at low temperature.[6] The material was unequivocally identified as a betaine which can be drawn in the conventional manner as **10**.[10] The compound is hydrolytically unstable to acid, decomposing on silica gel

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(1) (a) Castro, J. L.; Matassa, V. G.; Broughton, H. B.; Mosley, R. T.; Street, L. J.; Baker, R. *BioMed. Chem. Lett.* **1993**, *3*, 993. (b) Castro, J. L.; Matassa, V. G. *Tetrahedron Lett.* **1993**, *34*, 4705.

(2) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172.

(3) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

(4) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(5) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(6) The complete details of the crystal structure results and quantum mechanical calculations on betaine **10** will be presented in a subsequent publication.

(7) In the case of **6**, no evidence of formation of coupled product or other side products was observed. In the case of **5**, however, at least two unidentified side products were present, as well as starting alcohol (53%), but neither of them appeared to contain the cyclic sulfamide moiety.

(8) (a) Etter, M. C.; Gillard, R. D.; Gleason, W. D.; Rasmussen, J. K.; Duerst, R. W.; Johnson, R. B. *J. Org. Chem.* **1986**, *51*, 5405. (b) Etter, M. C.; Baures, P. W. *J. Am. Chem. Soc.* **1988**, *110*, 639. (c) Etter, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 2586.

(9) Betaine **10** is not soluble in THF or DMF but is soluble in CH_2Cl_2 or $CHCl_3$.

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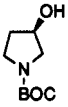
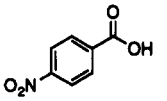
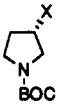
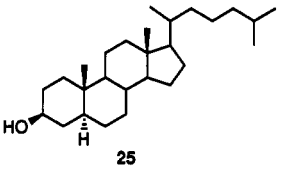
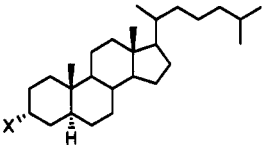
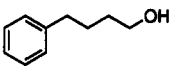
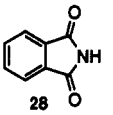
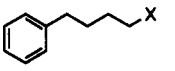
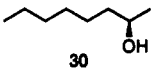
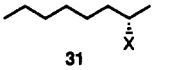
Table 1. Utilization of betaine 10 in Mitsunobu-like Processes[a]

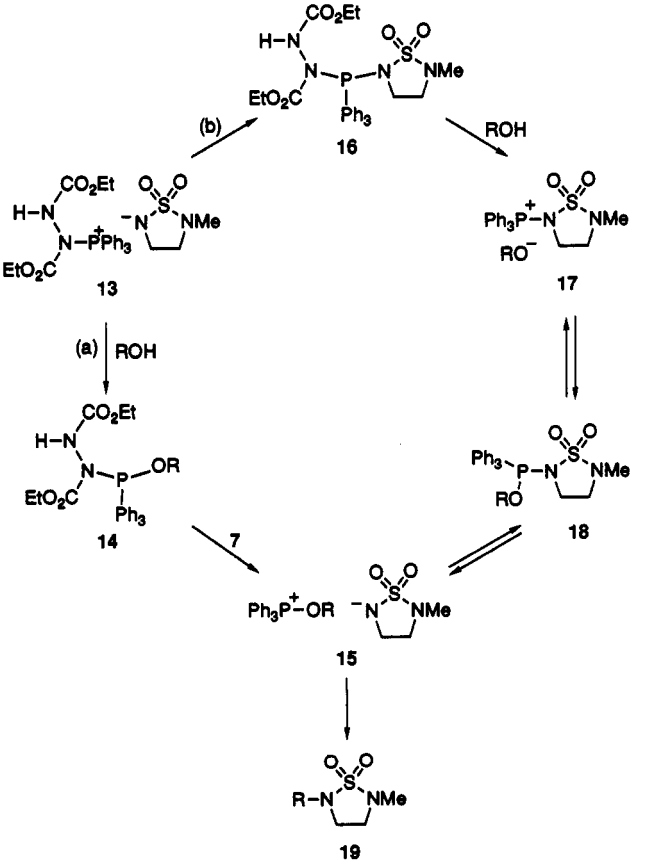
entry	substrate	HX	condns	product	yield[b] (%)
1	 22	 23	CH_2Cl_2, rt, 5 h	 24	89
2	 25	23	CH_2Cl_2, rt, 64 h	 26	53
3	25	23	Toluene, rt, 17 h	26	95
4	 27	 28	CH_2Cl_2, rt, 2.5 h	 29	98
5	 30	28	CH_2Cl_2, rt, 65 h	 31	80

[a] All reactions were carried out using 1.5 equiv of 10, 1.5 equiv of HX, and 1.0 equiv of alcohol. [b] Unoptimized isolated yields.

to TPPO and 8, but it can be stored in the solid state for several months without significant degradation. A proposal for the formation of 10 is shown in Scheme 1: initial generation of the familiar TPP–DEAD complex 11 followed by proton transfer from 8 would give ion pair 12. Intermolecular migration of the TPP group to the cyclic sulfamide and a second proton abstraction by the DEAD component would afford 10 and reduced DEAD. It is noteworthy that formation of betaine 10 does not require the necessary intervention of the alcohol, and indeed, the adduct can be prepared quantitatively by addition of DEAD (1 equiv) to a solution of 8 (1 equiv) and TPP (1 equiv) in THF at rt.[11]

When only one proton on the cyclic sulfamide is available for transfer (e.g., 7), the betaine cannot, of course, be formed. In those cases, the initial ion pair 13 can either follow the usually accepted mechanistic pathway[12] (a, Scheme 2) or alternatively decompose to a new ion pair 17 which, because it cannot form a zwitterionic species, eventually converts to 15 (through the intermediacy of 18[13]) and finally to the coupled product 19. The extremely facile formation of betaine 10, in this case helped by its

Scheme 2



low solubility characteristics in THF, would appear to indicate that the second pathway (b, Scheme 2) might be favored and that, perhaps, a similar mechanism could be operative in Mitsunobu couplings involving other acidic

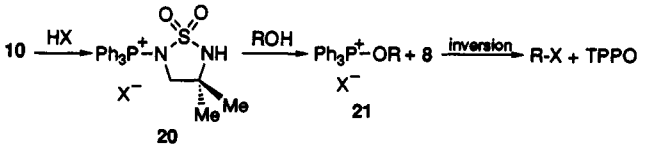
(10) Formation of betaine 10 closely resembles the generation of *N*-acylphospha-λ^5-azenes and sulfonylphospha-λ^5-azanes from primary amides and primary sulfonamides, under similar Mitsunobu conditions: Bittner, S.; Assaf, Y.; Krief, P.; Pomerantz, M.; Ziemnicka, B. T.; Smith, C. G. *J. Org. Chem.* **1985**, *50*, 1712.

(11) **Betaine 10.** To a stirred solution of Ph_3P (8.73 g, 33.28 mmol) and 8 (5.0 g, 33.28 mmol) in anhyd THF (100 mL) was added dropwise, over 10 min, DEAD (5.25 mL, 33.28 mmol) under nitrogen. The mixture was stirred at rt for 3 h, and the white solid was collected by filtration, washed with anhyd THF (20 mL) and anhyd Et_2O (2 × 20 mL), and dried over P_2O_5 under high vacuum to give 13.2 g (96%) of 10: mp 169–172 °C (CH_2Cl_2–MeCN; dec); ^{31}P-NMR (DMSO-d_6) δ 27.96 (relative to 85% H_3PO_4). Anal. Calcd for $C_{22}H_{23}N_2O_2PS$: C, 64.37; H, 5.65 N, 6.82. Found: C, 64.43; H, 5.58; N, 6.69.

(12) For mechanistic studies of the Mitsunobu reaction see: (a) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235. (b) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. (c) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257. (d) Camp, C.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045. (e) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049. (f) Kodaka, M.; Tomohiro, T.; Okuno, H. *J. Chem. Soc., Chem. Commun.* **1993**, 81.

(13) The pentacoordinate phosphorous species 18 would be analogous to the (acyloxy)alkoxyphosphoranes proposed by Camp and Jenkins.[12e] In our case, however, it would appear to arise from alkoxide addition to phosphonium salt 17 rather than by addition of the cyclic sulfamide anion to oxyphosphonium salt 15.

Scheme 3



–NH– derivatives. Although further research will be needed in order to adequately substantiate this idea, the preferential formation of **16** over **14** could be the result of the enhanced nucleophilic character of the cyclic sulfamide anion compared to the alkoxide.

The inherent similarities between zwitterionic species **10** and **11** suggested the possibility of utilizing the former as a stable source of $[Ph_3P]^+$ in Mitsunobu-like processes (Scheme 3). Thus, the use of an acidic component HX with a pK_a lower than that of betaine **10** would generate ion pair **20**. Subsequent reaction with the alcohol ROH would then afford oxyphosphonium salt **21** and cyclic sulfamide **8**. Because of the acidic strength of HX, **8** would exist largely in the unionized form, and therefore, it would constitute a noncompeting nucleophile in the S_N2 displacement reaction leading to the product RX. Indeed, betaine **10** was found to promote the coupling of alcohols with carboxylic acids (Table 1, entries 1–3) in good to excellent isolated yields.[14] The reaction occurs, as expected, with Walden inversion of the alcohol,[15,16] and in certain cases the use of toluene can be advantageous (entry 3 *vs* entry 2).[16] Of particular interest is the observation that **10** is also highly effective in the alkylation of phthalimide with alcohols (entries 4 and 5), a process which likewise occurs with inversion of configuration.[17] In this case, the pK_a of the acid HX is only 3.9 pK_a units lower than **8** itself,[18] and one would anticipate that this difference is even smaller when compared to zwitterionic species **10**.

In conclusion, we have described the preparation and demonstrated the utility of betaine **10** in promoting the coupling of alcohols with acids and imides. The stability and simple preparation of this adduct suggest that it could be used as a convenient alternative to DEAD–TPP in these and several other related processes (lactonization, decarboxylative dehydration, etc.).[5,19]

Acknowledgment. We are grateful to Professors Ulf Ragnarsson (Uppsala University, Sweden) and Ilmar Koppel (Tartu University, Estonia) for kindly measuring the pK_a of **8** and to Mr. S. Thomas for the acquisition of ^{31}P-NMR spectra.

Supplementary Material Available: Experimental procedures and characterization data for compounds **8**, ***ent*-22**, **24**, **26**, **29**, **31**, and 2,5-bis(4-nitrobenzoyl)-3,3-dimethyl-1,2,5-thiadiazolidine 1,1-dioxide (2 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) **General Procedure for Mitsunobu-like Reactions Using Betaine 10.** To a stirred mixture of the alcohol (3.32 mmol) and HX (5.0 mmol) in anhyd solvent (30 mL) was added portionwise, over 10 min, adduct **10** (5.0 mmol), and the resulting clear (milky) solution was stirred at rt, under nitrogen, for several hours (see Table 1). Et_2O (150 mL) was added, and the organic phase was washed with water (40 mL), dilute aqueous K_2CO_3 (40 mL), and brine (40 mL) and then dried ($MgSO_4$) and concentrated. Products were purified by flash chromatography on silica gel (hexane–CH_2Cl_2 or hexane–EtOAc).

(15) Proof of the inversion of configuration of the alcohol was obtained by hydrolyzing the esters to the corresponding alcohols with LiOH or NaOH in MeOH–THF–H_2O and comparing the optical rotation or ^1H-NMR with those for the starting materials.

(16) A limitation of this method has been found, however, in the case of sterically congested alcohols. Thus, inversion of (–)-menthol with *p*-nitrobenzoic acid and **10** in toluene gave a 62:38 mixture (37% yield) of inverted and noninverted esters, respectively. The direct esterification of the alcohol can be explained by invoking the intermediacy of an (acyloxy)phosphonium salt formed by reaction of **20** with the carboxylate as a result of the slow alcohol activation step due to steric congestion. In these cases, formation of significant amounts 2,5-bis(4-nitrobenzoyl)-3,3-dimethyl-1,2,5-thiadiazolidine 1,1-dioxide was also observed. This side product was also produced during the inversion of (+)-dihydrocholesterol in CH_2Cl_2 but not in toluene.

(17) **(*S*)-(+)-2-Octylphthalimide (31):** colorless oil; $[\alpha]^{27}_D = +19.9°$ ($c = 3.16$, EtOH) [$[\alpha]^{20}_D = +19.0°$ ($c = 3.0$, EtOH): Harpp, D. N.; Adams, J.; Gleason, J. G.; Mullins, D.; Steliou, K. *Tetrahedon Lett.* **1978**, 3989].

(18) The pK_a of phthalimide measured in DMSO is 13.4 (see ref 2). Using the same experimental protocol the pK_a for the cyclic sulfamide **8** has been found to be 17.3.

(19) The fact that cyclic sulfamide **8** is not extracted from the aqueous layer with Et_2O during workup facilitates the isolation of the coupled products and might represent an added advantage over the use of DEAD–TPP.