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A thiazine-S-oxide, Staudinger/aza-Wittig based synthesis of benzodiazepines and benzothiadiazepines

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Abstract

A new approach to the synthesis of imine containing 1,2,5-benzothiadiazepine-1,1-dioxides and 1,4-benzodiazepin-5-ones using iminophosphoranyl thiazine-S-oxides as precursors is reported. Key steps include a Staudinger reaction, an aza-Wittig reaction and the conversion of a thiazine-S-oxide into an amino ketone via a [2,3] sigmatropic rearrangement.

Keywords: benzodiazepines; benzothiadiazepines; aza-Wittig reaction; thiazine-S-oxides.

Interest in the chemistry, synthesis and biology of the 1,4-benzodiazepine[1] pharmacophore and related heterocycles, such as the 1,2,5-benzothiadiazepines,[2] continues to be fuelled not only by their activity against a variety of CNS disorders, but also by a range of biological activities against other disease states. Amongst the imine containing systems of interest are pyrrolobenzodiazepine natural products[3,4] such as the antitumour antibiotic DC-81[5] **1**, and the pyrrolo-1,2,5-benzothiadiazepine **2**, which is representative of a novel class of non-nucleosidic reverse transcriptase inhibitors.[6] Amongst the many[1] tricyclic systems of interest are the 1,4-diazepines, such as nevirapine[7] **3** and the 1,2,5-thiadiazepines[8] such as compound **4**, which show activity as non-nucleosidic inhibitors of reverse transcriptase (Fig. 1).

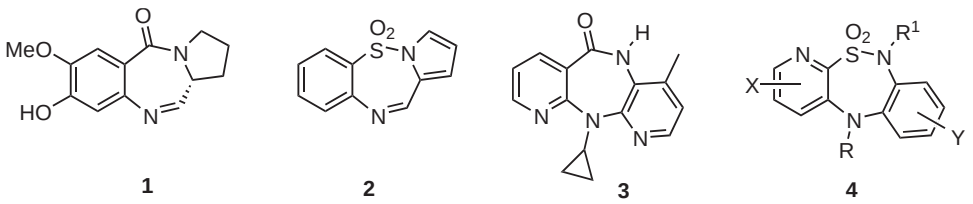

Figure 1.

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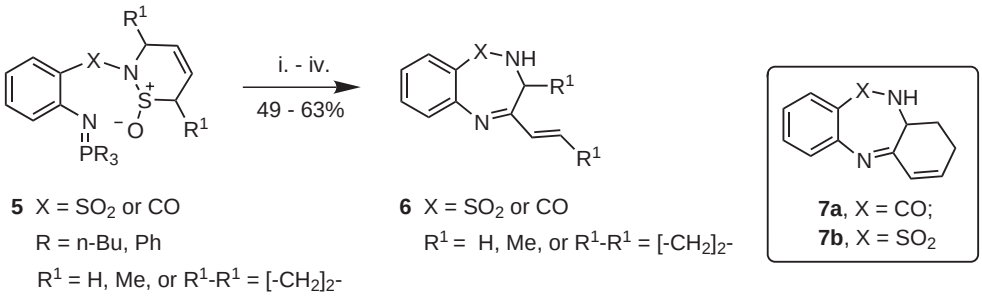
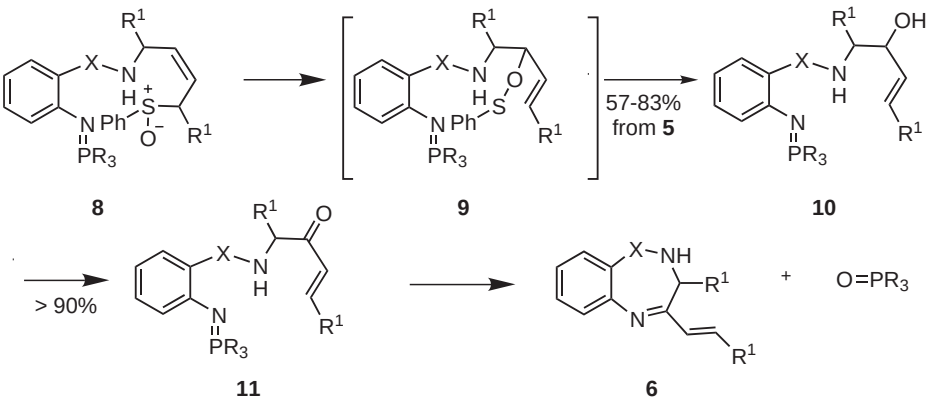
We wish to report herein a four step synthetic protocol, summarised in Scheme 1, by which the imine containing 1,4-benzodiazepines and 1,2,5-benzothiadiazepines **6** are accessed from iminophosphoranyl thiazine-S-oxides[9] **5**. As an example, our route allows access to the tricyclic fused systems **7a** and **7b** in 49 and 57% yields from the thiazine-S-oxides **5** (X = CO or SO_2; R = *n*-Bu; R^1–R^1 = –$[CH_2]_2$–).



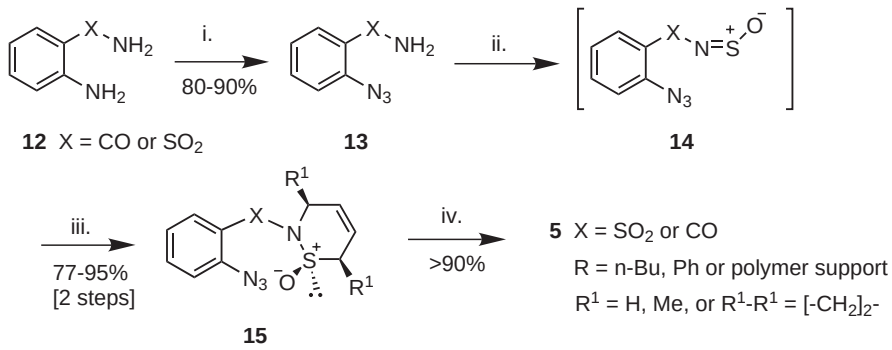
Scheme 1. Reagents and conditions: (i) 2.1 equiv. PhMgBr, THF, –40°C then aqueous work up; (ii) $P(OMe)_3$, MeOH, 60°C; (iii) Dess–Martin oxidation; (iv) toluene or xylene, reflux

The details of the synthesis are summarised in Scheme 2. Thus, the reaction of the thiazine-S-oxides **5** (R = Bu; X = CO or SO_2; R^1 = H, Me or R^1–R^1 = –$[CH_2]_2$–) with phenyl magnesium bromide gave the allylic sulfoxides **8**, which were used without further purification. Treatment of the allylic sulfoxides **8** with hot methanolic trimethyl phosphite under rigorously dry conditions resulted in the expected[9,10] [2,3] sigmatropic rearrangement, which furnished the alcohols **10** via the intermediate sulfenate esters **9**. Alcohols **10** were isolated in good yield, and were converted into the ketones **11** by Dess–Martin oxidation[11] using the sodium thiosulfate work-up procedure.[12] Ketones **11** were heated in boiling toluene or xylene, whereupon intramolecular aza-Wittig reaction[13,14] furnished the desired heterocycles **6** (X = CO or SO_2; R^1 = H, Me or R^1–R^1 = –$[CH_2]_2$–) in 49–63% overall yield from the thiazine-S-oxides **5**. With the triphenyl derived iminophosphoranyl thiazine-S-oxides **5** (R = Ph; X = CO or SO_2; R^1 = H, Me), we observed hydrolysis of the iminophosphorane functionality, indicative of the greater reactivity of the P-aryl iminophosphoranes.[13,15] We are currently exploring the use of the polystyryldiphenylphosphine polymer supported system **5** (R = polystyrene polymer support), which should allow transfer of the chemistry in Schemes 1 and 2 to the solid phase.[16] This offers future potential for the generation of combinatorial libraries of benzodiazepines, an area of continuing interest.[17–22]



Scheme 2.

The thiazine-S-oxides **5** required for this work were readily available, as shown in Scheme 3. Thus, the reaction of *o*-aminobenzamide or *o*-aminobenzenesulfonamide **12** with HONO, followed by treatment with sodium azide, furnished the azides **13** in excellent yields. Treatment of compounds **13** with thionyl chloride[23,24] gave the *N*-sulfinyl dienophiles **14** which underwent in situ hetero Diels–Alder reaction to give the adducts **15**, as single diastereoisomers where relevant, in 77–95% yield from **13**. The stereochemistry of adducts **15** were determined by X-ray crystallographic studies. Treatment of the azide functionality of adducts **15** with either triphenylphosphine, tri-*n*-butylphosphine or polystyrene supported triphenylphosphine[25] resulted in near quantitative Staudinger reaction[15] to yield the desired iminophosphoranyl thiazine-S-oxides **5**.



Scheme 3. Reagents and conditions: (i) c.HCl (aq.), $NaNO_2$, 0°C; then NaN_3, H_2O, NaOAc; (ii) 1.1 equiv. of $SOCl_2$, 6 equiv. of pyridine, CH_2Cl_2, 25°C, 4 hours; (iii) $R^1CH{=}CH{-}CH{=}CHR^1$, CH_2Cl_2, 25°C, 18 hours; (iv) PR_3 (see text), toluene or THF

In summary, we have developed a reliable synthesis of benzodiazepines and benzothiadiazepines **6** starting from readily accessible iminophosphoranyl thiazine-S-oxides. Our synthesis relies upon the conversion of the thiazine-S-oxide functionality into an amino ketone, followed by aza-Wittig reaction to furnish the heterocycle. We are currently developing the chemistry of thiazine-S-oxides to allow an entry into the pyrrolobenzodiazepines and pyrrolobenzothiadiazepines, and are also expanding our route to include the synthesis and use of chiral, non-racemic thiazine-S-oxides.

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