Trithiadiazepyne

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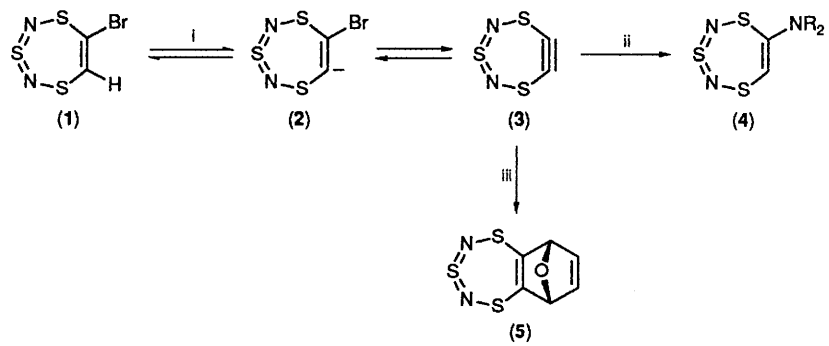
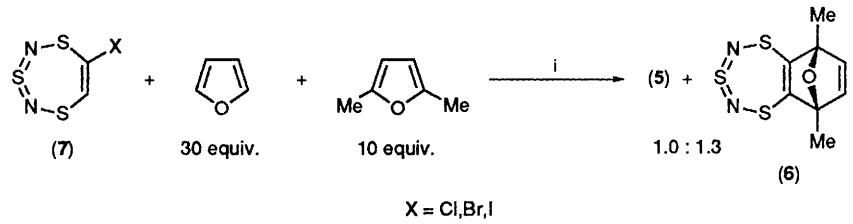
6,7-Didehydrotrithiadiazepine (trithiadiazepyne) (**3**) is readily generated from 6-bromotrithiadiazepine (**1**) with Hünig's base or sodium methoxide, and is intercepted in high yield by dienes and nucleophiles; formation of the highly stabilised carbanion (**2**) and the hetaryne (**3**) are established by deuterium exchange, competition experiments, and generation of (**3**) from 6-chloro-, -bromo-, and -iodo-trithiadiazepine.

We have shown that 6-bromotrithiadiazepine (**1**) reacts with ammonia and amines to give 6-aminotrithiadiazepines (**4**) in very mild conditions.[1] The absence of a strong base, and of cycloadduct formation in the presence of furan, appeared to disfavour an elimination–addition mechanism *via* the hetaryne (**3**). However, 6,7-dibromotrithiadiazepine and 7-bromotrithiatriazepine, which lack an *ortho*- hydrogen, were completely inert to amines and so the elimination of hydrogen bromide from (**1**) had to be considered, and the acidity of the ring proton in (**1**) was estimated by hydrogen–deuterium exchange.

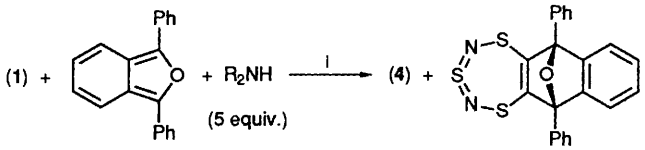
When bromide (**1**) was treated with 5 equiv. of morpholine in tetrahydrofuran (THF) containing an excess of deuterium oxide at room temperature for 5 h, deuteriation was extensive in both the morpholino product (**4**, NR_2 = morpholino) (90% D for H) and the recovered bromide (**1**) (80% D for H) at 75%



Scheme 1. *Reagents*: i, $EtNPr^i_2$ or NaOMe, MeOH, 20 °C; ii, R_2NH; iii, furan.

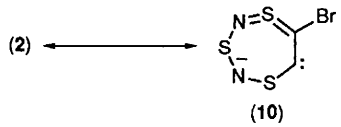


Scheme 2. *Reagents*: i, $EtNPr^i_2$, MeOH, 20 °C.



	(4)	(9)
Morpholine	74%	3%
Di-isopropylamine	54%	11%
Tetramethylpiperidine	0%	76%

Scheme 3. *Reagents*: i, THF, 20 °C.



reaction. Similarly, when 6-bromo-7-deuteriotrithiadiazepine was treated with morpholine in THF at room temperature the product and the recovered starting material were extensively de-deuteriated (>90% at 70% reaction). Thus, the ring proton of (**1**) is sufficiently acidic for the hetaryne mechanism to be operative, and the absence of the furan cycloadduct in the amine reactions could have resulted from greater reactivity of the amines in intercepting the aryne (**3**).

When bromide (**1**) was treated with the non-nucleophilic base *N*-ethyldi-isopropylamine (Hünig's base) and furan in THF at room temperature the cycloadduct (**5**) was indeed formed, but the reaction was slow requiring several days for completion. We noticed that the deuterium exchange reactions, catalysed by Hünig's base, were much faster than cycloadduct formation, and D_2O and H_2O were found to have a marked accelerating effect on the latter. Water caused some decomposition of the bromide (**1**) but methanol had the same accelerating effect without this disadvantage, and it could be used as solvent. The reactions were clean and fast in dry methanol, being complete within 10 min at room temperature with 2 equiv. of Hünig's base; the hetaryne (**3**) was trapped with a variety of 1,3-dienes in the yields shown (Table 1). With cyclopentadiene the trapping is nearly quantitative. In the absence of base no reaction occurred between bromide (**1**) and the dienes; unsubstituted trithiadiazepine has previously been shown to be inert towards a range of dienes under forcing conditions.[2]

The elimination–addition mechanism now seemed more reasonable. It was supported by the formation of 6-anilinotrithiadiazepine (**4**, NR_2 = NHPh) from bromide (**1**) and aniline in THF in the presence, but not in the absence, of Hünig's base, the stronger base being required to generate the hetaryne (**3**) which is then intercepted by aniline.

Table 1. Formation of cycloadducts analogous to (**5**) from bromide (**1**), a diene, and Hünig's base or sodium methoxide in methanol at 20 °C.

	Cycloadduct		% Yield	
Diene		M.p. (*T*/°C)	With $EtNPr^i_2$	With NaOMe
Furan	(**5**)	56—57	54	73
2-Methylfuran		41—42	—	79
2,5-Dimethylfuran	(**6**)	Oil	60	75
2,3-Dimethylbutadiene		140—141	66	—
6,6-Dimethylfulvene		95—96	70	—
1,3-Diphenylisobenzofuran	(**9**)	214—216	83	92
Cyclopentadiene		Oil	94	—

No 6-methoxytrithiadiazepine (**7**, X = OMe) was formed in the cycloaddition reactions in methanol, the aryne presumably being insufficiently electrophilic to react with methanol. Sodium methoxide in methanol did react with bromide (**1**) to form 6-methoxytrithiadiazepine, but only in low yield (30%), and so a cycloaddition reaction was attempted with sodium methoxide as base. A dilute solution of 2.5 equiv. of NaOMe in MeOH, added to the bromide and a diene over 30 min, gave improved yields of cycloadducts (Table 1), and this is the preferred method for the generation and trapping of hetaryne (**3**) with electron rich dienes.

The high symmetry of the hetaryne (**3**) presumably enhances its stability, but the absence of substituents removes one of the easier ways of establishing the involvement of an (unsymmetrical) aryne. We, therefore, investigated structural changes in the aryne precursor and the diene, and performed some competition experiments, to confirm the reaction pathway.

Furan and 2,5-dimethylfuran were allowed to compete for the aryne generated from the chloro-, bromo-, and iodotrithiadiazepines (**7**) (Scheme 2). Their molar ratio was adjusted to give approximately equal amounts of the two cycloadducts (**5**) and (**6**), which were carefully estimated by ^1H NMR studies on the total reaction products. The three ratios were identical within experimental error, and are actually closer than related figures for benzyne cycloadditions.[3] Thus, the same species is presumably undergoing the Diels–Alder reactions in each case, and hetaryne (**3**) seems to be the only reasonable candidate.

We also studied competition between the reactive diene, 1,3-diphenylisobenzofuran (**8**), and three amines of widely different nucleophilicities in THF, with the results shown in Scheme 3. The strong nucleophile morpholine gave almost

exclusively the morpholino derivative, the weak nucleophile di-isopropylamine gave the di-isopropylamino derivative together with some isobenzofuran cycloadduct (**9**), and the non-nucleophilic 2,2,6,6-tetramethylpiperidine gave exclusively the cycloadduct (**9**). The cycloadduct (**9**) was shown not to react with the amines used. These results support the involvement of an intermediate that is intercepted in both Diels–Alder and nucleophilic addition reactions.

These, and other,[4] results lead most reasonably to the mechanism of Scheme 1 where the hetaryne (**3**) is formed reversibly, but reacts irreversibly with amines and dienes. The most striking aspect is the initial formation of the carbanion (**2**) under such mild conditions. Why is it so stable? One possibility is extensive delocalisation of the negative charge onto the heteroatoms of the polarisable 10π aromatic ring, leaving a carbenoid contribution on carbon (**10**). This is similar to the well known stabilisation of analogous carbanions on five-membered heteroaromatics such as thiazoles and thiadiazoles.[5] The carbanionic centre will presumably be stabilised by the adjacent sulphur atom; it is also antiperiplanar to polarisable C–S and S–N bonds and there could be significant overlap between their σ* antibonding orbitals and the carbanion. The rate of aryne formation is much greater in methanol than THF and so the carbanion may also be stabilised by hydrogen bonding; hydrogen bonding solvation of the departing bromide and the ring heteroatoms, thus activating proton loss, could also contribute.

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