REACTION OF 1,2,4-TRIAZINE 1-OXIDES WITH BENZYNE : FORMATION OF 1,3-BENZOXAZEPINE AND 1,3,5,6-BENZOXATRIAZONINE DERIVATIVES

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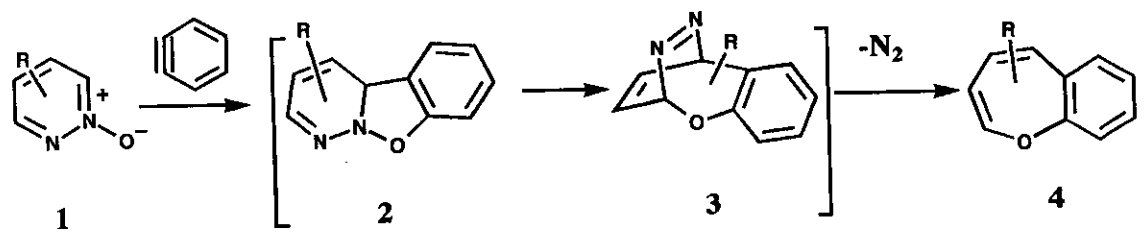
Abstract - Reaction of the 6-unsubstituted 1,2,4-triazine 1-oxides (**5**) with benzyne gave the 1,3-benzoxazepines (**8**) and / or the 6-(*o*-hydroxyphenyl)-1,2,4-triazines (**10**) *via* the unisolable 1,3-dipolar cycloadducts (**6**), whereas the 6-substituted compound (**12**), 5,6-dimethyl-3-methoxy-1,2,4-triazine 1-oxide, afforded only the relatively stable 1,5-shift product (**15**) derived from the initially formed 1,3-dipolar cycloadduct (**13**). Heating the adduct (**15**) gave the novel 1,3,5,6-benzoxatriazonine derivative (**16**) and 2,3-dimethylbenzofuran (**17**).

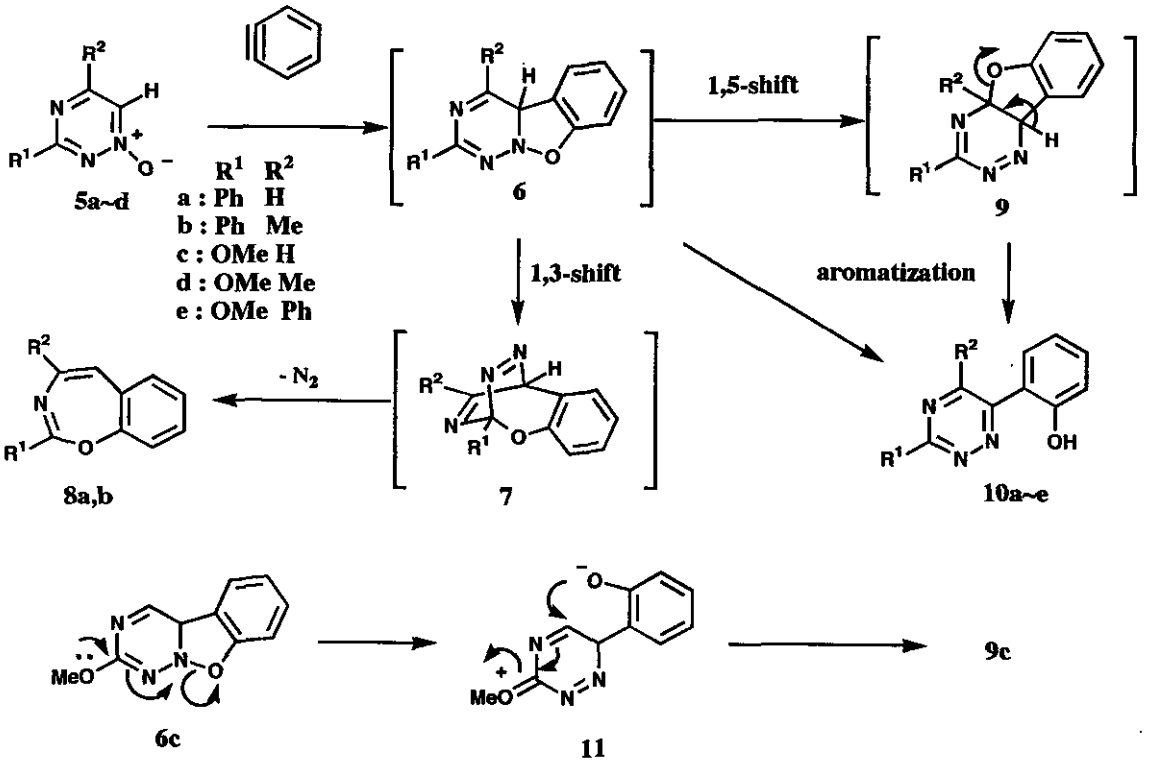
1,3-Dipolar cycloadditions are known in general to form initially five-membered ring adducts, which sometimes undergo further reactions to give a variety of secondary products.[1] We have also found that the 1,3-dipolar cycloaddition of pyridazine *N*-oxides (**1**) with benzyne resulted in the formation of the 1-benzoxepines (**4**) *via* the initially formed unisolable cycloadducts (**2**) and their 1,3-shift intermediates (**3**),[2] and that various benzyne analogues such as pyridynes,[3] quinolynes[3] and didehydrotropones[4] reacted similarly with **1** to give the corresponding novel fused oxepines. These results prompted us to examine the reaction of benzyne with 1,2,4-triazine 1-oxides instead of pyridazine *N*-oxides (**1**). We report here the formation of 1,3-benzoxazepines and a novel nine-membered 1,3,5,6-oxatriazonine ring compound. Although many synthetic routes to fully unsaturated monocyclic 1,3-oxazepines are known, only two routes to 1,3-benzoxazepines have been reported. They are based on the photochemical rearrangement with



Scheme 1

ring expansion of isoquinoline *N*-oxides[5] or by the intramolecular aza-Wittig reaction of the iminophosphoranes derived from *o*-acyloxyazidocinnamates.[6]

Treatment of the 6-unsubstituted 3-phenyl-1,2,4-triazine 1-oxides (**5a,b**)[7] with a large excess of benzyne, generated *in situ* from anthranilic acid by diazotization with isoamyl nitrite in tetrahydrofuran in the presence of a catalytic amount of trifluoroacetic acid, gave the expected 1,3-benzoxazepines (**8a,b**)[8] in 15~20% yields, together with the 6-(*o*-hydroxyphenyl)-1,2,4-triazines (**10a,b**) in 30~40% yields.[9] Whereas the 3-methoxy-1,2,4-triazine 1-oxides (**5c~e**), [10] upon treatment with benzyne, afforded only the phenolic compounds (**10c~e**) in 40~50% yields without any 1,3-benzoxazepines.

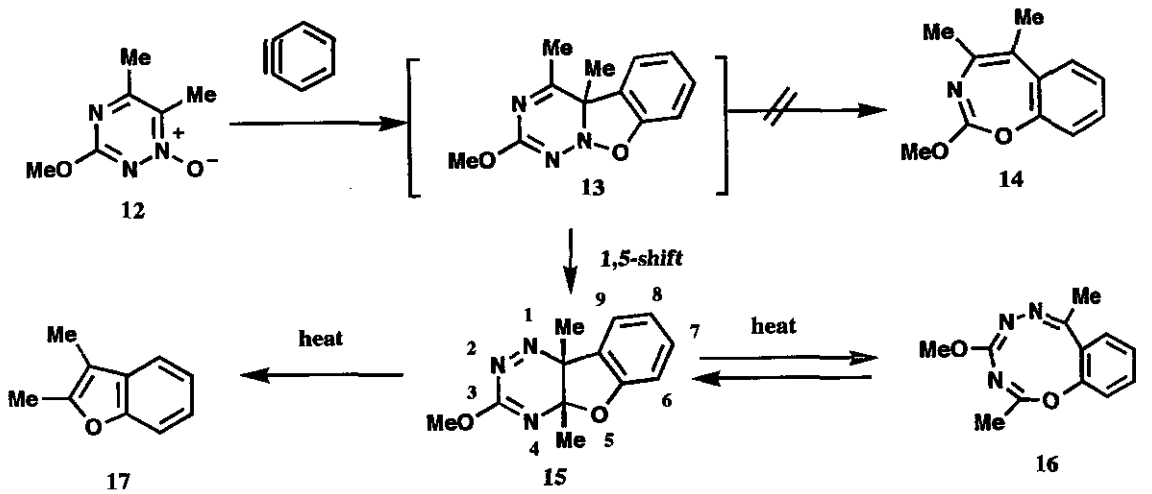


Scheme 2

A possible mechanism for the reactions is shown in Scheme 2. The 1,3-dipolar cycloadducts (**6**) initially formed may undergo N-O bond fission followed by competing 1,3- and 1,5-shift, and the aromatization with extrusion of the 6-proton. The 1,3-shift leads to the 1,3-benzoxazepines (**8**) *via* the intermediates (**7**), by analogy with the case of pyridazine *N*-oxides (**1**).[2~4] In the case of the methoxy compounds (**6c~e**), the 1,5-shift predominates to form the rearrangement intermediates (**9**), thus the oxazepines (**8c~e**) can not be

obtained. The electron-donating methoxy group may provide assistance for the formation of the 1,5-shift intermediates (**9**) by the actions illustrated in the structures (**6c**) and (**11**) in Scheme 2. The phenolic products (**10**) would be derived from either intermediates (**6**) or (**9**) by the aromatization.

Based on these results, next, we examined the reaction of benzyne with 3-methoxy-5,6-dimethyl-1,2,4-triazine 1-oxide (**12**), expecting that the absence of triazine ring proton could prevent the formation of the 1,3-adduct (**13**) from such aromatization. As expected, the 1,5-shift from the initially formed cycloadduct (**13**) took place predominantly to afford the shift product (**15**) in *ca.* 30% yield as the sole isolable compound,[11] and neither the benzoxazepine (**14**) nor phenolic compounds could be obtained.



Scheme 3

Heating the tricyclic compound (**15**) in refluxing toluene for 2.5 h gave a novel nine-membered ring compound (**16**), 2,7-dimethyl-4-methoxy-1,3,5,6-benzoxatriazonine,[12] and 2,3-dimethylbenzofuran (**17**) in 49% and 10% yields, respectively as well as the starting **15** (30% yield). All of the ring double bonds of the new ring system (**16**) were found to have *cis*-configuration by X-ray crystallographic analysis,[13] indicating that this ring-opening proceeds in the disrotatory fashion. It should be noted that on further heating in refluxing toluene, the isolated oxatriazonine (**16**) reverted to the tricyclic compound (**15**) (*ca.* 30% yield) along with the benzofuran (**17**) (9% yield) and the starting (**16**) (55% yield), showing that **15** and **16** exist in thermal equilibrium. The benzofuran (**17**) may be formed from **15** by extrusion of nitrogen and a nitrile moiety.

The reaction of 1,2,4-triazine 1-oxides with benzyne is concluded to offer us a variety of products including a novel heterocyclic ring compound, thus the similar reactions of other triazine *N*-oxides are now under investigaion.

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9. Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds reported. **10a** : Yellow needles, mp 185~187 ℃ ; **10b** : yellow needles, mp 228~230 ℃ ; **10c** : colorless needles, mp 116~118 ℃ ; **10d** : yellow needles, mp 165~167 ℃ ; **10e** : yellow needles, mp 172~173 ℃.
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11. **15** : Orange needles, mp 82~85 ℃. ^{1}H-Nmr ($CDCl_3$) δ : 1.53 (3H, s, 9b-Me), 1.84 (3H, s, 4a-Me), 3.95 (3H, s, 3-MeO), 6.81~7.41 (4H, m, Ar-H). ^{13}C-Nmr ($CDCl_3$) δ : 156.1 (s, 3-C), 148.9 (s, 5a-C), 130.0 (d, 9-C), 129.3 (s, 9a-C), 124.7 (d, 7-C), 121.7 (d, 8-C), 110.4 (d, 6-C), 94.1 (s, 4a-C), 74.6 (s, 9b-C), 54.9 (q, 3-MeO), 24.2 and 21.2 (q, 9b- and 4a-Me).
12. **16** : Colorless prisms, mp 150~152 ℃. ^{1}H-Nmr ($CDCl_3$) δ : 2.20 (3H, s, 2-Me), 2.40 (3H, s, 7-Me), 3.26 (3H, s, 4-MeO), 6.92~7.46 (4H, m, Ar-H). ^{13}C-Nmr ($CDCl_3$) δ : 158.0 (s, 4-C), 155.1 (s, 2-C), 146.6 (s, 7-C), 146.3 (s, 11a-C), 130.6 (s, 7a-C), 129.8 (d, 8-C), 127.4 (d, 10-C), 125.9 (d, 9-C), 120.7 (d, 11-C), 54.0 (q, 4-MeO), 23.3 (q, 7-Me), 22.3 (q, 2-Me).

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