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Novel Conversion of Selenium-containing Five-membered Aromatics to Nitrogen-containing Six-membered Aromatics via Hetero Diels-Alder Reaction with Acetylenic Dienophiles

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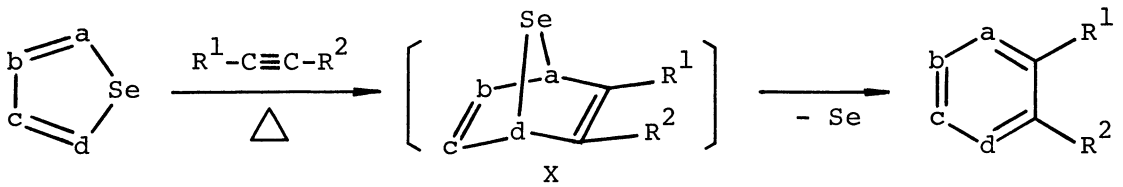
Treatment of selenium-containing five-membered heteroaromatics with acetylenic dienophiles afforded several nitrogen heterocycles in good to moderate yields by using thermal reaction conditions. These reactions were thought to proceed through sequential [4+2] cycloaddition-selenium extrusion pathway.

Recently Diels-Alder reactions of cyclic heterodienes have become one of the most effective methods for the syntheses of various heterocycles.[1,2] In all cases heteroatoms such as N, O, and S atoms in the starting aromatic compounds behave as removable bridges of heterodienes fixed in cisoid form.[3,4] However, synthetic applications of these sequences to construct complicated compounds have been extremely limited owing to their drastic reaction conditions. On the other hand, it was assumed that selenium analogues of these substrates would behave as more reactive cyclic heterodienes because of the weak C-Se or N-Se bond and enhanced ring strain of the heterocycles,[5,6] and that the subsequent heteroatom extrusion would be also improved.[7,8] From such a standpoint, we have reported a novel preparation of primary selenoamides,[9] from which several selenium-containing heterocycles such as 3,5-disubstituted 1,2,4-selenadiazoles were easily available by the reported

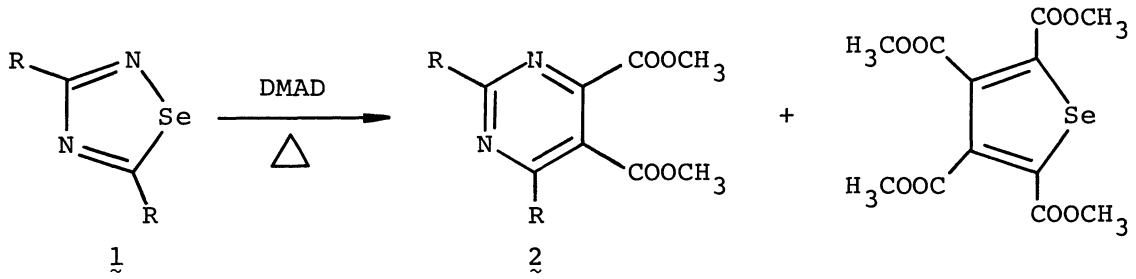


a, b, c, d = C, Heteroatom

methods.[10-12] In this paper we would like to describe a novel conversion of selenium-containing heteroaromatics to the corresponding nitrogen heterocycles by treating with acetylenic dienophiles in thermal conditions.

A typical procedure in the reaction of 3,5-disubstituted 1,2,4-selenadiazoles 1 with dimethyl acetylenedicarboxylate (DMAD) is as follows. A 143 mg (0.5 mmol) of 3,5-diphenyl-1,2,4-selenadiazole (1a) and 710 mg (5.0 mmol) of DMAD was heated in autoclave to 150 °C for 12 h. The reaction mixture was then poured into $CHCl_3$, and the precipitated elemental selenium was separated by filtration. After removal of the solvent, the residue was separated by SiO_2 column chromatography to give dimethyl 3,5-diphenyl-5,6-pyrimidinedicarboxylate (2a) in 54% yield together with selenophene derivative[13] (38%) and the substrate 1a (14%). In contrast with their sulfur analogues,[14] this procedure was successfully applied to various 3,5-disubstituted 1,2,4-selenadiazoles 1 possessing not only aromatic but also aliphatic and heteroatomic substituents. The structures of all products were confirmed by ^1H NMR, IR, MS, and elemental analysis, and by the comparison of their physical properties with those reported by Cherkasov et al.[15] All results of the reactions of 1,2,4-selenadiazoles 1 with DMAD or methyl propiolate are shown in Table 1.

Table 1. Conversion of 3,5-disubstituted 1,2,4-selenadiazoles to pyrimidine derivatives



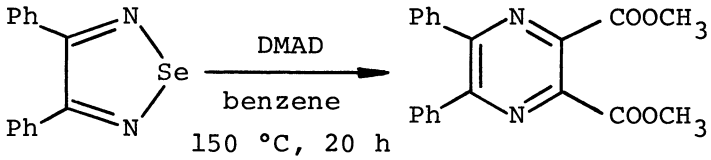
1 2

Run	R		Solvent	Temp/°C	Time/h	Yield/% of 2
1	C_6H_5	1a	neat	150	12	54
2	4-$CH_3C_6H_4$	1b	neat	150	10	46
3	4-$CH_3OC_6H_4$	1c	$CHCl_3$	reflux	110	31
4	4-$CH_3OC_6H_4$	1c	neat	150	10	73
5	4-ClC_6H_4	1d	neat	150	12	17
6	n-C_3H_7	1e	benzene[a]	150	15	24
7	n-C_5H_{11}	1f	xylene	reflux	11	74
8	n-C_7H_{15}	1g	xylene	reflux	43	87
9	$PhCH_2S$	1h	toluene	reflux	14	19
10	$(CH_3)_2N$	1i	benzene	r.t.	2	99

a) The reaction was carried out in autoclave.

The reaction of 1i (R=$(CH_3)_2N$) with DMAD proceeded at room temperature to afford the product 2i in almost quantitative yield, and even a less reactive dienophile such as methyl propiolate reacted with 1i at 120 °C for 12 h (in benzene in autoclave) to afford 3[16] in quantitative yield in a highly regioselective manner as was expected from FMO theory. In contrast, phenylacethylene, methyl 3-phenylpropiolate, maleic anhydride, or TCNE, did not react at all below 200 °C, and prolonged reaction time in the elevated temperature caused decomposition of the starting material 1a to benzonitrile and 2,4,6-triphenyl-1,3,5-triazine. From these results, it was easily assumed that a combination of heterodienes with higher HOMO energy levels and dienophiles with lower LUMO levels was actually needed for the conversion of 1,2,4-selenadiazoles 1 to the corresponding pyrimidines 2. Thus, the primary stage of the reaction was regarded as a typical [4+2] cycloaddtion reaction with an ordinary electron-demand, and the resulting selenium-containing bicyclic intermediate X was thought to cause facile selenium-extrusion to afford pyrimidine 2 and elemental selenium.

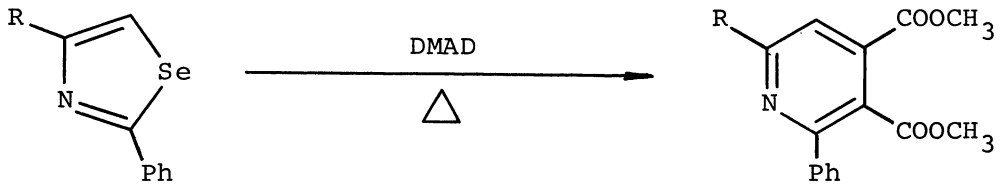
Similar reactions were also carried out by treatment of 3,4-diphenyl-1,2,5-selenadiazole (4) or 2-substituted 4-phenyl-1,3-selenazoles 6 with DMAD, and in all cases the corresponding pyrazine 5 or pyridine derivatives 7, were obtained in moderate yields. These results are also shown in Scheme 1 and Table 2.



4 5 (16%)

Scheme 1.

Table 2. Conversion of 2-Substituted 4-Phenyl-1,3-Selenazoles to Pyridine Derivatives[a)]



6 7

Run	R		Solvent	Temp/°C	Time/h	Yield/% of 7
1	C_6H_5	6a	neat	100	78	47
2	C_6H_5	6a	benzene	150	82	53
3	4-$CH_3C_6H_4$	6b	benzene	150	24	55
4	4-$CH_3OC_6H_4$	6c	benzene	150	24	55
5	4-ClC_6H_4	6d	benzene	150	24	41

a) The reaction was carried out in autoclave.

In conclusion, it has become apparent that selenadiazoles and selenazoles behaved as reactive cyclic azadienes bridged by selenium atoms, and these selenium-containing heterocycles underwent facile [4+2] cycloaddition with reactive dienophiles and subsequent selenium extrusion to afford nitrogen heterocycles in good to moderate yields. Novel applications of the sequence to the syntheses of several complicated heterocycles are now in progress in our laboratory.

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14) When treated with DMAD at 200 °C for 10 h, 3,5-diphenyl-1,2,4-thiadiazole was completely recovered.
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16) Methyl 2,4-bis(dimethylamino)-5-pyrimidinecarboxylate (3): pale yellow plates, mp 72.5-73.0 °C, MS(m/z): 224(M^+, ^{80}Se), IR(KBr): 2890, 1710, 1555, 1380, 1160, 1080, 1005, 790 cm^{-1}, ^1H NMR($CDCl_3$): δ 3.02(6H, s), 31.18(6H, s), 3.81(3H, s), 8.54(1H, s). In the NOE experiments of 3, a slight enhancement was observed in the proton resonances at the ester methyl group upon irradiation to the dimethylamino proton resonances (3.02 ppm). Found: C, 53.78; H, 7.23; N, 24.95%. Calcd for $C_{10}H_{16}N_4$: C, 53.50; H, 7.18; N, 25.03%.

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