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An efficient 1,3-dipolar cycloaddition between aromatic selenoaldehydes and nitrile oxides or nitrile imines: an easy access to selenium-containing five-membered heterocyclic ring system

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Abstract—1,3-Dipolar cycloaddition between aromatic selenoaldehydes, generated by thermal retro Diels-Alder reaction of anthracene cycloadducts, and nitrile oxides or nitrile imines proceeded efficiently to give the corresponding [3+2] cycloadducts as a single isomer in good yields, being 1,4,2-oxaselenazoles or 1,3,4-selenadiazoles, respectively.

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Selenocarbonyl compounds are very reactive selenium analogues of carbonyl compounds and play an increasingly important role in organic synthesis. Among them selenoaldehydes and selenoketones have been well recognized to serve as significant 2π dienophiles in cycloaddition reactions. In this context, cycloaddition of the reactive selenoaldehydes is an important approach to the preparations of selenium-containing heterocycles which have been recently paid much attention because of their interesting reactivities and their potential biological applications. In the course of our studies for generation and reaction of reactive selenoaldehydes, we have developed an efficient method for the generation of selenoaldehydes under neutral conditions via thermal retro Diels-Alder reaction of selenoaldehyde-anthracene cycloadducts 1 that were easily synthesized in good yields from the reaction of the corresponding aldehydes with (Me₂Al)₂Se in the presence of anthracene (Scheme 1). We have already reported the reactions of selenoaldehydes with oxygen-functionalized conjugated dienes, 2-methoxymuran, and 5-ethoxypyrazoles using the above retro Diels-Alder protocol.

Keywords: Selenoaldehyde; 1,3-Dipolar cycloaddition; Nitrile oxide; Nitrile imine; Selenium-containing heterocycle.

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On the other hand, 1,3-dipolar cycloaddition has been considered to be the most useful method for the construction of five-membered heterocyclic ring systems containing one or more heteroatoms. Selenoaldehydes serve as an excellent dienophile as mentioned above and would also have a high potential as a good dipolarophile. Indeed 1,3-dipolar cycloaddition between selenoaldehydes and a stable nitrile oxide (2,4,6-trimethylbenzonitrile N-oxide) has been already reported. However, to our knowledge, up to date there are no reports regarding 1,3-dipolar cycloaddition of other 1,3-dipoles with selenoaldehydes. We have carried out the reaction of selenobenzaldehyde, generated by our thermal retro Diels-Alder reaction of 1 (R=Ph), with some popular 1,3-dipoles such as nitrones, nitrile oxides, azomethine ylides, and nitronates, but only reaction with nitrile oxides gave the corresponding [3+2] cycloadducts of the selenoaldehyde in good yields as isolable compounds. This result may indicate that efficient [3+2] cycloaddition reaction of selenoaldehydes can be achieved by using a linear-type 1,3-dipole such as nitrile oxide. In this paper we describe an efficient 1,3-dipolar cycloaddition between aromatic selenoaldehydes and nitrile oxides or nitrile imines as a
linear-type 1,3-dipole to afford selenium-containing five-membered ring products, 1,4,2-oxaselenazoles or 1,3,4-selenadiazoles, respectively.

Most nitrile oxides are short-lived and reactive species, and easily dimerize, rearrange, or polymerize. At first, we used a stable aromatic nitrile oxide, 2,4,6-trimethylbenzonitrile N-oxide, easily prepared through two steps from 2,4,6-trimethylbenzaldehyde. The toluene solution of 1 (R=Ph) and the stable nitrile oxide was heated at reflux for 30 min to give the desired [3+2] cycloadduct (2a) as a single isomer in 85% yield (Eq. (1)). The structure of this adduct was supported by the analysis of the NMR mass spectra. In particular, regiochemistry of the cycloadduct was confirmed by the mass spectrum which showed a fragment peak at $m/z$ 225 with an isotope pattern involving one selenium atom, corresponding to [M-PhCHO] as shown in Scheme 2. This indicates that a carbon-oxygen bond exists in the obtained cycloadduct, being 1,4,2-oxaselenazole.

Several anthracene cycloadducts with an aromatic substituent were similarly treated with 2,4,6-trimethylbenzonitrile N-oxide in toluene at reflux for 30 min to give the corresponding [3+2] cycloadducts (2) as a single isomer in good yields. The results are shown in Table 1. Mass spectra of all cycloadducts showed a same fragment peak pattern at $m/z$ 225 that is corresponding to [M-ArCHO], which indicates all obtained cycloadducts have 1,4,2-oxaselenazole skeleton. Anthracene cycloadducts having an aliphatic group did not undergo retro Diels-Alder reaction at toluene reflux temperature, but at over 150°C, the generation of aliphatic selenoaldehydes was efficient. Thus, we examined the reaction of 1 (R=n-Pr and CH₂CH₂CH₃Ph) with the nitrile oxide at 160°C in toluene, but no isolable cycloadducts could be obtained from the reaction mixture.

Next we planned the reaction of selenoaldehydes with unstable nitrile oxides which are in situ formed via dehydrochlorination of hydroximoyl chlorides with triethylamine as a base. Generally, this dehydrochlorination has to be carried out in the presence of the dipolarophile, since the lifetime of the reactive nitrile oxide is too short for isolation. However selenoaldehydes, being a dipolarophile in this research, are also much more reactive and very unstable. Accordingly, both selenoaldehyde and nitrile oxide must be efficiently in situ generated in the reaction mixture simultaneously. After several trials under different conditions, we found a following reaction procedure for an efficient 1,3-dipolar cycloaddition. After 6 equiv of triethylamine was added to a toluene solution of 1 (R=Ar) and 3 equiv of aromatic hydroximoyl chloride at room temperature, the reaction vessel was immediately placed for 30 min into oil bath preheated at 110°C. The results are summarized in Table 2. In all cases, an efficient 1,3-dipolar cycloaddition proceeded to give the desired [3+2] cycloadducts (3), 1,4,2-oxaselenazoles, as a single regiosomer in good yields. They were very stable at room temperature in the atmosphere. The regiochemistry of the obtained [3+2] cycloadducts was the same as the case using 2,4,6-trimethylbenzonitrile N-oxide, that is, the mass spectra of

<table>
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<th>Entry</th>
<th>Ar</th>
<th>Cycloadduct</th>
<th>Yield (%)a</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>3a</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>naphthyl</td>
<td>3b</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>p-CF₃C₆H₄</td>
<td>3c</td>
<td>94</td>
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<tr>
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</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>3e</td>
<td>76</td>
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<tr>
<td>6</td>
<td>p-CF₃C₆H₄</td>
<td>3f</td>
<td>58</td>
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</tbody>
</table>

* Isolated yield.
the cycloadducts showed a fragment peak corresponding to [M-ArCHO]⁺.

The reaction of selenoaldehydes with unstable aliphatic nitro oxide did not give a satisfactory result, but the use of a stable aliphatic nitro oxide, 2,2,3-tri phenylpropanenitrile N-oxide,¹⁶ resulted in the excellent result as shown in Eq. 2. In this case, the [3+2] cycloadduct was obtained in excellent yield as a single isomer with the same regiochemical result as mentioned above.

In conclusion, we have demonstrated that regioselective 1,3-dipolar cycloaddition between aromatic selenoaldehydes, generated from 1 via thermal retro Diels-Alder reaction, and nitro oxides or nitro imines proceeded efficiently to afford the [3+2] cycloadducts, 1,4,2-oxaselenazoles or 1,3,4-selenadiazoles, respectively, in good yields. This method offered a promising prospect for building up selenium-containing five-membered heterocyclic ring system. We are currently extending the scope of 1,3-dipolar cycloaddition between seleno aldehydes and other 1,3-dipoles. The results of our findings will be reported in due course.

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References


14. Typical experimental procedure: To an oven dried 30 mL round bottomed flask fitted with a reflux condenser were added an anthracene cycladduct (1, 0.5 mmol), hydroximoyl chloride (1.5 mmol), and toluene (15 mL) under an argon atmosphere. This mixture was then stirred until all of the solids dissolved at room temperature. Once a clear solution was obtained, triethylamine (3.0 mmol) was added to the reaction mixture, and the reaction vessel was immediately placed into an oil bath preheated at 110°C. After the heating at 110°C for 30 min, the mixture was allowed to cool to room temperature and evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel with 40:1 hexane / ethyl acetate to give the desired cycladduct 3 as a single isomer. Selected spectral data of [3+2] Cycladducts 3. Compound 3a: 1H NMR (400 MHz, CDCl₃): δ 2.27 (s, 3H), 6.93 (d, 2H), 7.76-7.78 (m, 3H), 7.52-7.56 (m, 2H), 7.54 (s, 1H), 7.59 (d, 2H); Mass (EI mode): m/z (relative intensity) 51 (21.4), 77 (61.4), 90 (42.5), 103 (31.4), 105 (66.2), 106 (66.2), 133 (100), 213 (24.6), 319 (M⁺, 3.2); HRMS calcd for C₁₃H₁₈N₂O₅Se (M⁺) 319.0112, found 319.0109.

15. Compound 3c: 1H NMR (400 MHz, CDCl₃): δ 3.84 (s, 3H), 6.91 (d, 2H), 7.57 (s, 1H), 7.59 (d, 2H), 7.63 (s, 4H); Mass (EI mode): m/z (relative intensity) 90 (32.0), 103 (22.2), 133 (100), 145 (64.9), 173 (73.0), 174 (53.9), 198 (22.0), 211 (21.9), 213 (44.7), 387 (M⁺, 8.6); HRMS calcd for C₂₄H₂₄N₄O₆Se (M⁺) 386.9985, found 386.9981, Compound 3d: 1H NMR (400 MHz, CDCl₃): δ 7.37 (d, 2H), 7.44 (s, 1H), 7.45-7.55 (m, 5H), 7.58 (d, 2H); Mass (EI mode): m/z (relative intensity) 77 (21.1), 105 (20.6), 137 (50.0), 176 (31.2), 215 (20.2), 217 (43.3), 246 (100), 248 (65.3), 323 (M⁺, 4.7); HRMS calcd for C₁₉H₁₈NO₂Se (M⁺) 322.9616, found 322.9626.

16. 15N NMR (76.2 MHz, CDCl₃): δ −12.5; HRMS calcd for C₂₁H₁₆O₇N₅Se (M⁺) 345.0984, found 345.0983, Compound 3e: 1H NMR (400 MHz, CDCl₃): δ 7.41 (d, 2H), 7.51 (s, 1H), 7.55 (d, 2H); Mass (EI mode): m/z (relative intensity) 211 (100), 233 (50.0), 246 (22.2), 364 (M⁺, 44.2); HRMS calcd for C₂₃H₂₂N₄O₆Se (M⁺) 364.0479, found 364.0481, Compound 4a: 1H NMR (400 MHz, CDCl₃): δ 6.87-6.90 (m, 9H), 7.02-7.47 (m, 9H), 7.10 (s, 1H), 7.55 (d, 2H), 7.63 (d, 2H); Mass (EI mode): m/z (relative intensity) 77 (80.2), 91 (88.7), 103 (33.7), 104 (100), 172 (49.1), 173 (21.3), 194 (25.3), 248 (53.3), 249 (52.2), 275 (46.7), 430 (23.8), 432 (M⁺, 47.8); HRMS calcd for C₂₃H₂₄N₆O₆Se (M⁺) 432.0353, found 432.0350, Compound 4d: 1H NMR (400 MHz, CDCl₃): δ 6.91-6.95 (m, 1H), 7.17-7.35 (m, 9H), 7.21 (s, 1H), 7.74 (d, 2H), 8.23 (d, 2H); Mass (EI mode): m/z (relative intensity) 77 (66.2), 91 (67.9), 104 (100), 105 (30.5), 180 (67.8), 181 (51.5), 252 (37.1), 409 (M⁺, 35.1); HRMS calcd for C₂₃H₂₄N₆O₆Se (M⁺) 409.0330, found 409.0329.