Pergamon

Tetrahedron Letters, Vol. 36, No. 2, pp. 237-240, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02229-1

Easy Access to Substituted Selenazine and Selenopyran Derivatives by a Cycloaddition-Cycloreversion Process.

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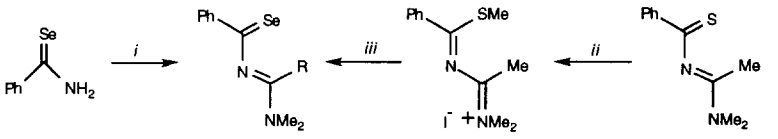
Abstract: N'-selenoacylamidines were isolated by condensation of selenobenzamide with orthoamides. [4+2] cycloadditions with electrophilic dienophiles were performed leading to 1,3-selenazine derivatives. Selenoamide vinylogs obtained by thermolysis of 4*H*-1,3-selenazines, were the precursors of functionalised selenopyrans or selenophenes.

The use of hetero Diels-Alder reactions in heterochemistry has been widely demonstrated.[1] In recent years, the synthesis of selenium heterocycles has been actively studied using carbon-selenium double bond as 2π dienophile intermediates for [4+2] cycloadditions.[2] Only few cycloadditions with selenodienic systems have been reported.[3] In this preliminary study we present an efficient route towards selenazine and selenopyran derivatives by [4+2] cycloadditions from N'-selenoacylamidines and selenoamide vinylogs respectively.

We prepared the selenobenzamide **1** by a modified Takikawa procedure.[4a] Bis-trimethylsilyl selenide[4b] reacted with benzonitrile in absence of solvent at 80°C in sealed tube affording **1** in 80% yield. Easier access to **1**, produced in 90% yield from benzonitrile, was also performed using sodium hydrogen selenide as proposed by Reid[5] (PhCN, NaSeH 4 eq., Py., 80°C, 1 hr.).

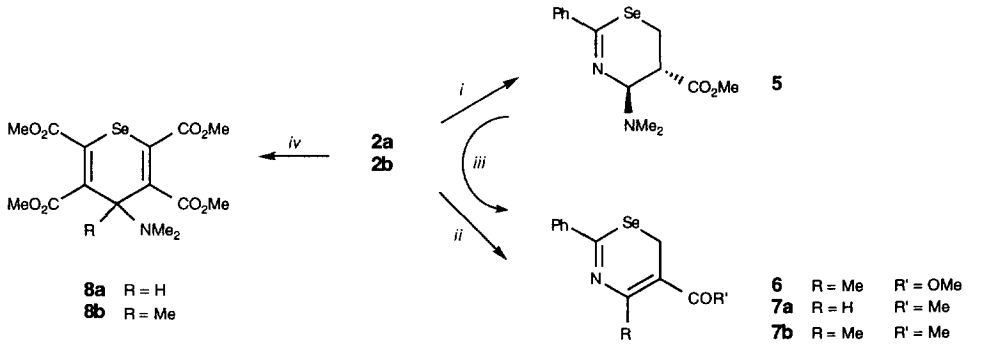
Following the experimental conditions previously described for the synthesis of N'-thioacylamidine **3** from thiobenzamide[6], condensation of selenobenzamide **1** with N,N'-dimethylformamide dimethyl acetal and with N,N'-dimethylacetamide dimethyl acetal, led to the corresponding N'-selenoacylamidines **2a** and **2b** in 30% and 90% yield respectively[7] (^{1}H NMR of the crude product of the reaction with **2a**, before the purification on silica gel, shown its presence in 80% yield in the mixture). Furthermore **3** can be considered as a potential precursor of **2b** *via* a 3-methylthio-2-aza-propeniminium salt **4** obtained quantitatively from **3** by addition of methyl iodide. Reaction of **4** with sodium hydrogen selenide afforded **2b** in 50% yield.[8]



1 **2a** R = H **2b** R = Me **4** **3**

i) for **2a**: $(MeO)_2C(H)NMe_2$ (1.3eq.), CH_2Cl_2, O°C, 1.5 hrs; for **2b**: $(MeO)_2C(Me)NMe_2$ (1.5eq.), CH_2Cl_2, r.t.,1.5 hrs.; *ii*) MeI (10eq.); *iii*) Py., NaSeH, EtOH reflux, 0.5 hr.

These results prompted us to investigate the reactivity of **2a** and **2b** in [4+2] cycloadditions with electrophilic dienophiles. Addition of **2a** with an excess of methyl acrylate (MA) at room temperature, afforded 5,6-dihydro-4*H*-1,3-selenazine **5** in 40% yield based on **1**. The cycloaddition of **2b** in methyl acrylate at 80°C, was followed by the elimination of dimethylamino group, giving the 6*H*-1,3-selenazine **6** in 50% overall yield. Cycloaddition-elimination has also been observed with methyl vinyl ketone (MVK) as dienophile and **2a** or **2b**, affording 6*H*-1,3-selenazines **7a** and **7b** in 65% yield respectively.[9]



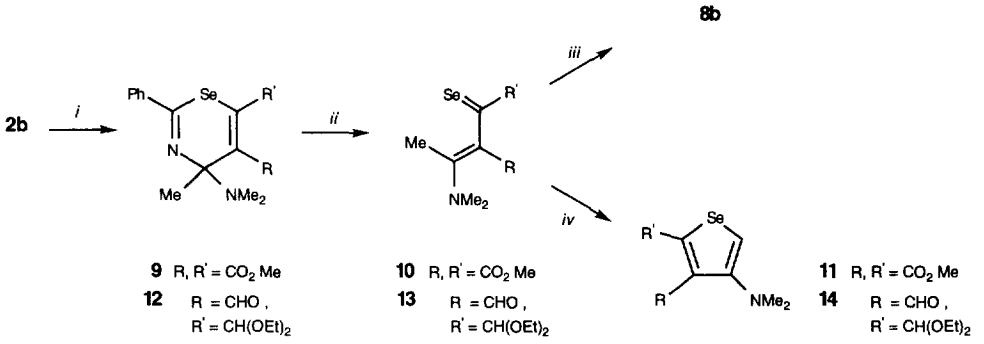
8a R = H **8b** R = Me

i) **2a**, MA (10eq.), CH_2Cl_2, r.t., 5 hrs.; *ii*) for **6**: **2b**, MA (10eq.) reflux, 20 hrs.; for **7a**: **2a**, MVK (10eq.), THF, r.t., 4 hrs.; for **7b**: **2b**, MVK (10eq.), THF reflux, 8 hrs.; *iii*) MVK (20eq.), CH_2Cl_2 reflux, 20 hrs ; *iv*) for **8a**: DMAD (10eq.), CH_2Cl_2, 0°C, 20hrs., for **8b**: *idem* at 40°C.

Access to **7a** can also be performed from dihydro-4*H*-1,3-selenazine **5**, *via* **2a**, in 70% yield by a retro-Diels-Alder and [4 + 2] cycloaddition sequence in presence of an excess of methyl vinyl ketone.

The reaction of N'-selenoacylamidines with dimethyl acetylenedicarboxylate (DMAD) was then studied. Addition of dimethyl acetylenedicarboxylate to **2a** and **2b** afforded 4*H*-selenopyrans **8a** and **8b** isolated in 45% and 60% overall yield respectively.[10] The obtention of 4*H*-selenopyrans **8** from **2** by a

cycloaddition-cycloreversion-cycloaddition process was confirmed by the analysis of the intermediates isolated in the synthesis of **8b**. [4 + 2] cycloaddition of **2b** with dimethyl acetylenedicarboxylate at 0°C gave the 4*H*-1,3-selenazine **9** in 58% yield. Thermolysis of **9** at 40°C led to the functionalised selenoamide vinylog **10** in 90% yield. Access to 4*H*-selenopyran **8b** was achieved from **10** in 55% yield by [4+2] cycloaddition with an excess of dimethyl acetylenedicarboxylate. Moreover in ethanol, the selenoamide vinylogs **10** can also be converted, to the selenophene **11** in 75% yield. Similar results were obtained with 4,4-diethoxy-2-butyn-1-al (DEBA) as dienophile. The selenophene **14** was synthetised from **2b** *via* the 4*H*-1,3-selenazine **12** (88% yield) and the selenoamide vinylog **13** (64% yield). ^{1}H and ^{13}C NMR data of compounds **9** to **14** are in accord with the proposed structures.[11]



i) for **9**: DMAD (1.5eq.), THF, 0°C, 1.5 hrs.; for **12**: DEBA (2eq.), CH_2Cl_2, 0°C, 1 hr.; *ii*) CH_2Cl_2 reflux, 15 hrs.; *iii*) DMAD (1.5eq.), CH_2Cl_2, 5°C, 0.5 hr.; *iv*) EtOH reflux, 12hrs.

In order to evaluate the influence of selenium atom in [4 + 2] cycloaddition, the reactivity of N'-selenoacylamidine **2b** was compared to its analog N'-thioacylamidine **3** which showed a similar configuration and conformation in the solid state.[12] A mixture containing **2b** (1 mmol) and **3** (1 mmol), was stirred at 20°C in THF for 1.5 hours in the presence of dimethyl acetylenedicarboxylate (1 mmol). The resulting cycloadduct, isolated in 80% yield, was identified as the 4*H*-1,3-selenazine **9**. Unreacted **3** was recovered after purification by flash chromatography. The higher reactivity of the N'-selenoacylamidine could be analysed on the basis of a predominant HOMO diene / LUMO dienophile interaction determinated by semi empirical calculations using PM3 method.[13] Therefore thermolysis of 4*H*-1,3-selenazine **9** was easier than with the corresponding 4*H*-1,3-thiazine analog.[14]

In summary, N'-selenoacylamidines and selenoamide vinylogs can be considered as substituted 3-aza-1-selenobutadienes and 1-selenobutadienes respectively for [4 + 2] cycloadditions under mild conditions. Cycloaddition-cycloreversion or reverse appear as an efficient way to transform N'-selenoacylamidines into selenoamide vinylogs or 4*H*-1,3-selenazines into 4*H*-selenopyran derivatives.

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4. a) Shimada, K.; Hikage, S.; Takeishi, Y.; Takikawa, Y. *Chem. Lett.*, **1990**, 1403-1406 and references therein. b) Detty, M. R.; Seidler, M. D. *J. Org. Chem.*, **1982**, *47*, 1354-1356.
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6. Tea, G. C.; Chehna, M.; Pradère, J. P.; Duguay, G.; Toupet, L. *Phosphorus and Sulfur*; **1986**, *27*, 327-339.
7. Spectral data for **2a** and **2b** : **2a** ^{1}H NMR (CD_3COCD_3, 90MHz): δ 3.24 (1s, 3H), 3.36 (1s, 3H), 8.68 (1s,1H), **2b** m.p. 123-125°C, ^{1}H NMR (CD_3COCD_3, 300MHz): δ 2.47 (1s, 3H), 3.20 (1s, 3H), 3.41 (1s, 3H), ^{13} C NMR (CD_3COCD_3, 75.47MHz): δ 19.4, 39.8, 40.4, 128.1, 129.4, 131.0, 146.0, 173.4 and 196.4. for X-Ray data see reference 12
8. Experimental conditions: **4** (6 mmoles) dissolved in 12ml of pyridine was added at room temperature to a solution of NaSeH generated *in situ* by addition of sodium borohydride (6 mmoles) in ethanol solution (40ml) containing selenium platelets (42 mmoles) at 0°C for 0.5 hour. The solution was heated at reflux of ethanol for another 0.5 hour. After extraction with AcOEt / HCl 0.1N, the organic layer was dried on $MgSO_4$ and evaporated. **2b** was isolated in 50% yield by flash chromatography on silica gel (AcOEt / petroleum ether : 20 / 80). A similar access to **2a** from a 3-chloro-2-aza-2-propeniminium salt has been proposed: see Liebsher, J. *Synthesis*, **1988**, 655-669.
9. Spectral data for **5, 6** and **7**: **5** ^{1}H NMR ($CDCl_3$, 200MHz): δ 2.41 (1s, 6H), 2.68 (m, J=12.3, 9.9, 4.3 Hz, 1H), 3.07 (1dd, J=11.0, 4.3 Hz, 1H), 3.61 (1dd, J=12.3, 11.0 Hz, 1H), 3.77 (1s, 3H), 4.22 (1d, J=9.9Hz, 1H), **6** ^{1}H NMR (CD_3COCD_3, 200MHz): δ 2.48 (1s, 3H), 3.64 (1s, 2H), 3.78 (1s, 3H), **7a** ^{1}H NMR (CD_3COCD_3, 90MHz): δ 2.47 (1s, 3H), 3.66 (1s, 2H), 8.13 (1s, 1H), ^{13}C NMR (CD_3COCD_3, 75.47MHz): δ 15.0, 26.0, 117.3, 129.7, 130.1, 133.5, 139.8, 149.9, 169.2 and 196.1, **7b** ^{1}H NMR (CD_3COCD_3, 90MHz): δ 2.40 (1s, 3H), 2.46 (1s, 3H), 3.68 (1s, 2H), ^{13}C NMR (CD_3COCD_3, 75.47MHz): δ 20.1, 22.4, 31.0, 114.6, 129.6, 130.3, 133.1, 139.6, 154.7, 164.6 and 198.9.
10. Spectral data for **8a** and **8b**: **8a** ^{1}H NMR (CD_3COCD_3, 300MHz): δ 2.26 (1s, 6H), 3.79 (1s, 6H), 3.83 (1s, 6H), 4.99 (1s, 1H), ^{13}C NMR (CD_3COCD_3, 75.47MHz): δ 41.3, 53.2, 53.8, 64.1, 131.2, 132.3, 165.2 and 167.6, **8b** ^{1}H NMR ($CDCl_3$; 200MHz): δ 1.94 (1s, 3H), 2.22 (1s, 6H), 3.78 (1s, 3H), 3.79 (1s, 3H), 3.80 (1s, 3H), 3.81 (1s, 3H).
11. Spectral data for **9** to **14** : **9** ^{1}H NMR ($CDCl_3$, 200MHz): δ 1.57 (1s, 3H), 2.39 (1s, 6H), 3.82 (1s, 3H), 3.86 (1s, 3H), **10** ^{1}H NMR ($CDCl_3$, 200MHz): δ 2.71 (1s, 3H), 3.58 (1s, 3H), 3.62 (1s, 3H), 3.67 (1s, 3H), 3.87 (1s, 3H), ^{13}C NMR ($CDCl_3$, 50.32MHz): δ 24.0, 43.7, 45.5, 52.0, 52.6, 120.7, 160.3, 172.0, 176.7 and 187.1, **11** ^{1}H NMR ($CDCl_3$, 200MHz): δ 2.65 (1s, 6H), 3.77 (1s, 3H), 3.86 (1s, 3H), 7.15 (1s, 1H), **12** ^{1}H NMR ($CDCl_3$, 200MHz): δ 1.23 (m, 6H), 1.59 (1s, 3H), 2.37 (1s, 6H), 3.70 (m, 4H), 5.62 (1s, 1H), 9.78 (1s, 1H), ^{13}C NMR ($CDCl_3$, 50.32MHz): δ 15.0, 15.1, 22.7, 39.1, 63.1, 63.5, 81.5, 98.5, 126.9, 128.5, 130.9, 134.4, 138.9, 143.2, 152.8, 189.7, **13** ^{1}H NMR ($CDCl_3$, 200MHz): δ 1.25 (m, 6H), 2.64 (1s, 3H), 3.40 (1s, 3H), 3.51 (1s, 3H), 3.70 (m, 4H), 5.49 (1s, 1H), 9.97 (1s, 1H), **14** ^{1}H NMR ($CDCl_3$, 200MHz): δ 1.23 (m, 6H), 2.73 (1s, 6H), 3.71 (m, 4H), 6.10 (1s, 1H), 6.99 (1s, 1H), 9.99 (1s, 1H), ^{13}C NMR ($CDCl_3$, 50.32MHz): δ 15.2, 45.6, 63.0, 98.1, 109.8, 132.8, 156.1, 162.6 and 187.1. Compounds **9**, **10**, **11**, **12** and **14** gave satisfactory elemental analysis.
12. The configuration of **2b** was established from X-Ray data (Toupet, L., Université de Rennes-I, France, unpublished results). For structural determination of N'-thioacylamidine see : Chehna, M.; Pradère, J. P.; Quiniou, H.; Le Botlan, D.; Toupet L. *Phosphorus, Sulfur and Silicon.*, **1989**, *42*, 15-19.
13. **2b**, HOMO -8.46 eV and LUMO -1.73 eV ; **3**, HOMO -8.94 eV and LUMO -1.48 eV. For PM3 calculations see Stewart, J. J. P. *J. Comp. Chem.* , **1989**, *10*, 209-220.
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(*Received in France* 10 *October* 1994; *accepted* 10 *November* 1994)