Pergamon

*Tetrahedron Letters*, Vol. 37, No. 45, pp. 8205-8208, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01868-0

# Intramolecular Diels-Alder Reaction of Pyrazines with an Alkenyl Side Chain

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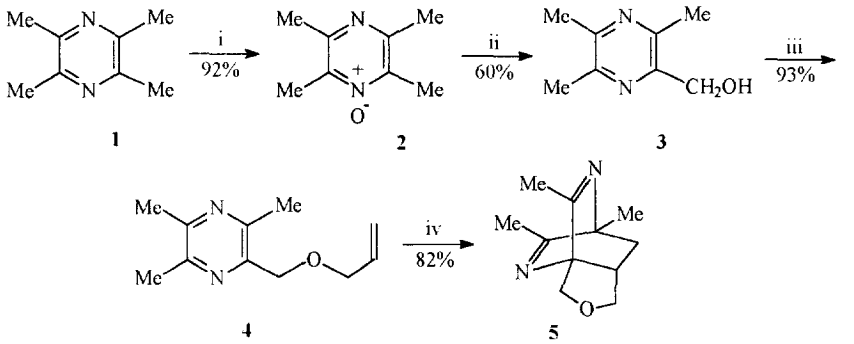
***Abstract***: Intramolecular Diels-Alder reaction of a series of pyrazines bearing a 5-membered-ω-alkene side chain in refluxing trifluoroacetic acid led to the formation of bridged tricyclic compounds. These cycloadducts underwent Retro Diels-Alder reaction in refluxing nitrobenzene to give original pyrazines.Copyright © 1996 Elsevier Science Ltd

Intramolecular Diels-Alder (IMDA) reactions[1] of pyrazines,[2] pyrimidines, 1,2,4-triazines and other electron-deficient heterocycles with an appropriate alkynyl moiety as side-chain dienophile have received considerable attention. The intermediate cycloadducts which were unable to be isolated underwent Retro Diels-Alder reaction to give terminal fused heterocycles or fused aromatic rings. This method provided flexible synthetic approaches to a variety of fused-ring compounds. On the other hand, few examples have been reported on the IMDA reactions of these heterocycles bearing an alkenyl side chain.[3] Most of these examples were concentrated on 1,2,4-trizines and the unstable cycloadducts were decomposed via Retro Diels-Alder reaction and oxidation to give fused pyridines. To our best knowledge, no literature has reported on the intramolecular Diels-Alder reaction of pyrazine with an alkenyl dienophilic side chain. Herein we report our study employing alkylpyrazines as azadienes with a $-CH_2-X-CH_2-CH=CH_2$ side chain (X=O, S, SO, $SO_2$).

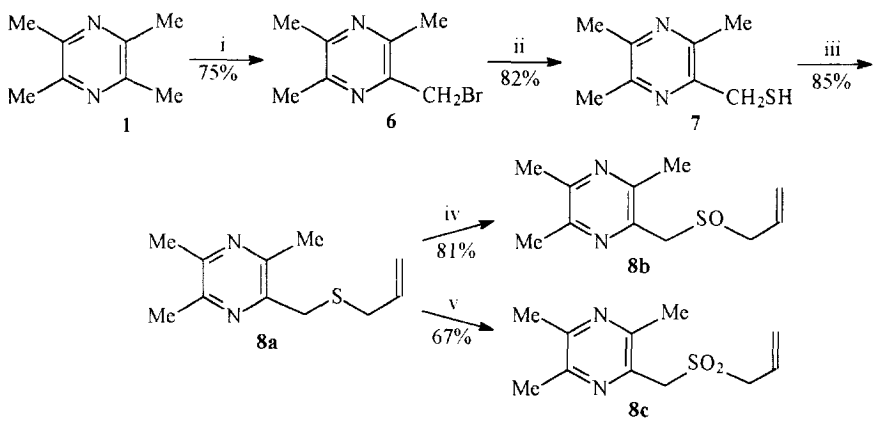
The synthesis of substrate **4** was summarized in Scheme 1. 2-Hydroxymethyl-3,5,6-trimethylpyrazine (**3**), conveniently prepared from tetramethylpyrazine (**1**),[4] was efficiently alkylated with allyl bromide to form compound **4** [5] using tetrabutylammonium bromide (TBAB) as a phase transfer catalyst.[6] Substrate **4** underwent intramolecular cycloaddition in refluxing trifluoroacetic acid (TFA)[7] for 2.5 hours to give bridged tricyclic compound **5**. This cycloaddition is the first example to our knowledge of the intramolecular inverse electron demand Diels-Alder reaction of pyrazines. The structure assignment of **5** was based on spectral evidence and its elemental analysis.[8]



i. $H_2O_2$, HOAc [4a]; ii. (1) $Ac_2O$, (2) $NaOH/H_2O$ [4b]; iii. $BrCH_2CH=CH_2$, TBAB [6]; iv. TFA [2c].

Scheme 1

In order to investigate the behavior of other alkylpyrazines carrying a 5-membered-ω-alkene side chain in this reaction condition, compounds **8a-c** [12] were prepared according to the route showed in Scheme 2.

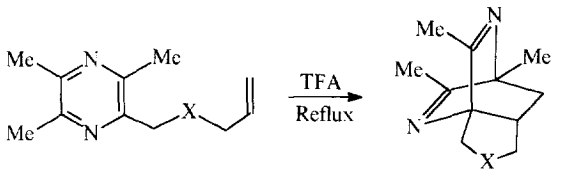


i. NBS, $(PhCO)_2O_2$, $CCl_4$; [5] ii. (1) $H_2NCSNH_2$, EtOH; (2) $NaOH/H_2O$; [9] iii. $BrCH_2CH=CH_2$, TBAB, 50%NaOH; iv. $NaIO_4$, $CH_3OH$; [10] v. m-CPBA, $CH_2Cl_2$ [11]

Scheme 2

Compounds **8a-c** were also found to undergo intramolecular cycloaddition in refluxing TFA, resulting in the formation of cycloadducts **9a-c** [12] (Scheme 3). From reaction time for the intramolecular cycloaddition of **4** and **8a-c**, it can be seen that the reactivity of the pyrazines increases in the order $X=SO_2 < X=SO < X=O < X=S$. This order showed that the reactivity of the pyrazines was largely depended on steric effect, not electric effect.

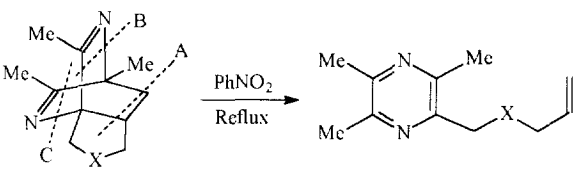
The molecule was able to form the favorite conformation to take place cycloaddition when X was S. Compound **8c** was the most difficult in the four pyrazines to form the ideal conformation to react.




| | | |
|---|---|---|
| **8a** (X=S) | 1h | **9a**, 75% |
| **8b** (X=SO) | 4h | **9b**, 68% |
| **8c** ($X=SO_2$) | 8h | **9c**, 78% |

Scheme 3

Taylor and Seitz found that the supposed tricyclic intermediates, formed by intramolecular cycloaddition of 1,2,4-triazines bearing an alkenyl side chain, could undergo nitrogen extrusion and dehydrogenation to aromatize to condensed pyridines under thermal conditions.[3a-d] Considering that these four cycloadducts **5** and **9a-c** might also aromatize to condensed pyridines through elimination of acetonitrile and oxidation at high temperature, we heated them in refluxing nitrobenzene. To our surprise, all of these four cycloadducts turned back into their original substrates **4** and **8a-c** via Retro Diels-Alder reaction (Scheme 4). The result demonstrated that these cycloadducts were unstable at high temperature and the cleavage in manner A was easier than that in manner B or C.




| | | |
|---|---|---|
| **5** (X=O) | 1h | **4**, 78% |
| **9a** (X=S) | 1h | **8a**, 80% |
| **9b** (X=SO) | 1h | **8b**, 67% |
| **9c** ($X=SO_2$) | 2h | **8c**, 71% |

Scheme 4

The presence of this Retro Diels-Alder reaction indicates that it was impossible for pyrazines carrying an alkenyl side-chain dienophile to give intramolecular Diels-Alder adducts at high temperature. In fact, heating compounds **4** and **8a-c** in refluxing nitrobenzene did not provide cycloadducts **5** and **9a-c** or condensed pyridines. If the compounds **4** and **8a-c** were heated at low temperature, only trace cycloadducts yielded.

In conclusion, our study showed that pyrazines as azadienes could react with appropriate alkenyl side chains in refluxing TFA to give cycloadducts and these cycloadducts returned to the original pyrazines at high temperature.

**Acknowledgment:** We would like to thank Professor Wei-Shan Zhou, Shanghai Institute of Organic Chemistry, for his useful discussions and suggestions for this work.

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7. It had been confirmed by van der Plas and his co-workers that TFA could protonate pyrazines so as to accelerate the intramolecular inverse electron demand Diels-Alder reaction of pyrazines [2e].
8. **5**: m.p. 134-5¡æ. $^1$H-NMR (300MHz, $CDCl_3$): 4.65, 4.28 (AB-q, J=8.5Hz, 2H), 3.95 (t, J=7.6Hz, 1H), 3.00 (dd, $J_1$=11.5Hz, $J_2$=7.6Hz, 1H), 2.11 (s, 6H), 2.02 (m, 1H), 1.80 (s, 3H), 1.40 (dd, $J_1$=12.4Hz, $J_2$=10Hz, 1H), 1.04 (dd, $J_1$=12.4Hz, $J_2$=5.5Hz, 1H). $^{13}$C-NMR-DEPT (300MHz, $CDCl_3$): 178.9, 173.5, 76.2, 66.6 (4×C); 44.5 (CH); 71.2, 70.5, 31.2 (3×$CH_2$); 21.8, 20.2, 19.5 (3×$CH_3$). EI-MS (m/e): 193 ($M^+$+1), 192 ($M^+$), 151, 136, 135, 121, 94, 82. IR ($cm^{-1}$): 2970, 2936, 2870, 1600, 1435, 1370, 1260, 1050, 1023, 890. UV ( $\lambda_{max}^{CH_3OH}$,nm): 205, 255. Anal. Calcd. for $C_{11}H_{16}N_2O$ (192.30): C 68.57, H 8.52, N 14.85; Found: C 68.70, H 8.39, N 14.57.
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12. Some data of compounds **7**, **8**, **9**: **7**: colorless liquid. $^1$H-NMR (300MHz, $CDCl_3$): 3.79 (d, 2H), 2.52 (s, 3H), 2.44 (s, 3H), 1.90 (t, 1H). **8a**: colorless liquid. $^1$H-NMR (300MHz, $CDCl_3$): 5.73-5.88 (br m, 1H), 5.20 (d, J=18.2Hz, 1H), 5.13 (d, J=10.0Hz, 1H), 3.74 (s, 2H), 3.14 (d, J=7.1Hz, 2H), 2.54 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H). **8b**: m.p. 83-4¡æ. $^1$H-NMR (300MHz, $CDCl_3$): 5.91-6.06 (br m, 1H), 5.50 (d, J=8.8Hz, 1H), 5.45 (d, J=17.0Hz, 1H), 4.20, 4.12 (AB-q, J=13.1Hz, 2H), 3.69 (q, 1H), 3.46 (q, 1H), 2.58 (s, 3H), 2.49 (s, 3H), 2.48 (s, 3H). **8c**: m.p. 102-3¡æ. $^1$H-NMR (300MHz, $CDCl_3$): 5.92-6.07 (br m, 1H), 5.64 (d, J=15.9Hz, 1H), 5.57 (d, J=10.1Hz, 1H), 4.39 (s, 2H), 3.82 (d, J=7.4Hz, 2H), 2.63 (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H). **9a**: m.p. 135-6¡æ. $^1$H-NMR (300MHz, $CDCl_3$): 3.63, 3.51 (AB-q, J=9.5Hz, 2H), 2.88 (dd, $J_1$=9.6Hz, $J_2$=7.1Hz, 2H), 2.20 (t, J=9.6Hz, 2H), 2.16 (s, 3H), 2.13 (s, 3H), 1.96 (m, 1H), 1.79 (s, 3H), 1.49 (dd, $J_1$=12.6Hz, $J_2$=9.6Hz, 1H), 1.11 (dd, $J_1$=12.6Hz, $J_2$=4.1Hz, 1H). **9b**: m.p. 149-150¡æ. $^1$H-NMR (300MHz, $CDCl_3$): 4.57, 3.10 (AB-q, J=13.3Hz, 2H), 2.91 (dd, $J_1$=12.8Hz, $J_2$=6.4Hz, 1H), 2.28 (t, J=12.8Hz, 1H), 2.20 (s, 3H), 2.07 (s, 3H), 1.81 (s, 3H), 1.67 (dd, $J_1$=12.7Hz, $J_2$=9.6Hz, 1H), 1.10 (dd, $J_1$=12.7Hz, $J_2$=4.4Hz, 1H). **9c**: m.p. 167-8¡æ. $^1$H-NMR (300MHZ, $CDCl_3$): 4.18, 3.72 (AB-q, J=9.5Hz, 2H), 3.23 (dd, $J_1$=12.1 Hz, $J_2$=6.8Hz, 1H), 2.57 (dd, $J_1$=13.4Hz, $J_2$=12.1Hz, 1H), 2.33 (m, 1H), 2.17 (s, 3H), 2.14 (s, 3H), 1.83 (s, 3H), 1.66 (dd, $J_1$=12.8Hz, $J_2$=9.7Hz, 1H), 1.12 (dd, $J_1$=12.8Hz, $J_2$=4.2Hz, 1H).


(*Received in China* 9 *May* 1996; *revised* 9 *July* 1996; *accepted* 8 *August* 1996)