Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 3895–3898

Novel intramolecular cyclization of 2-(buta-1,3-dienyl)-3-methylpyrazines and 3-(buta-1,3-dienyl)-4-methyl-1,2,5-oxadiazoles into 5*H*-cycloheptapyrazines and 4*H*-cyclohepta-1,2,5-oxadiazoles

Masakatsu Matsumoto,* Naoyuki Hoshiya, Ryo Isobe, Yukie Watanabe and Nobuko Watanabe

Department of Materials Science, Kanagawa University, Tsuchiya, Hiratsuka, Kanagawa 259-1293, Japan

Received 19 February 2004; revised 10 March 2004; accepted 19 March 2004

Abstract—2-(Buta-1,3-dienyl)-3-methylpyrazines (**5**) and 3-(buta-1,3-dienyl)-4-methyl-1,2,5-oxadiazoles (**10**) were synthesized starting from base-induced reaction of 2,3-dimethylpyrazine or 3,4-dimethyl-1,2,5-oxadiazole with α,β-unsaturated carbonyls. The thus obtained heteroaromatics bearing a butadienyl moiety and a methyl at the adjacent position underwent intramolecular cyclization by the action of LDA to give the corresponding heteroaromatics fused with a seven-membered ring [**7** (**8**)] and [**11** (**12**)] in moderate to high yields.
© 2004 Published by Elsevier Ltd.

One fundamental strategy to construct a seven-membered ring is the carbon–carbon bond formation between both termini of a C_7 carbon chain, as represented by intramolecular aldol reaction and Dieckmann condensation. For these types of intramolecular reaction, both reaction centers, namely, an anionic carbon and an electrophilic carbon, are in general separated from each other through saturated carbons, so that they are preliminarily little different from the intermolecular reaction of a carbanion aside from steric factors. On the other hand, little has been known of an intramolecular cyclization of a C_7-skeleton involving no saturated carbon, in which a carbanion at a terminus is conjugated formally with a hexa-1,3,5-triene unit to construct a C_7-8π-electron system.

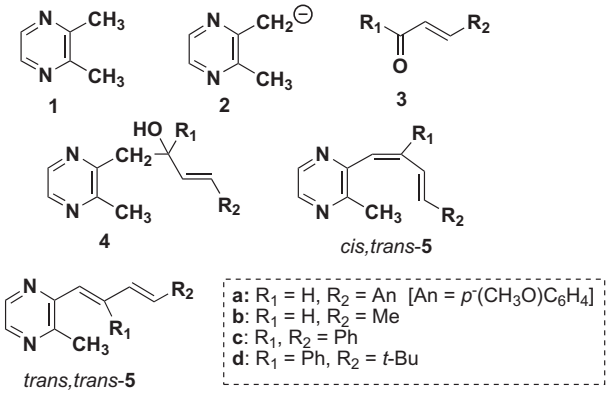
In the course of our investigation on homologation of 2,3-dimethylpyrazine and 3,4-dimethyl-1,2,5-oxadiazole, we found that such a cyclization into a seven-membered ring occurs effectively for a C_7-8π-electron system comprised of a buta-1,3-dienyl, an anionic methyl, and two adjacent sp^2-carbons of the aromatic heterocycles joining these two substituents.

Precursors of the formal C_7-8π-electron system now investigated, namely, 2-(buta-1,3-dienyl)-3-methylpyrazines (**5a–d**), were synthesized from 2,3-dimethylpyrazine (**1**) and α,β-unsaturated carbonyl compounds (**3a–d**) in several steps. The initial step was lithiation of 2,3-dimethylpyrazine (**1**) to a lithium salt of an anion (**2**), which was easily attained by the use of butyllithium[1–3] or lithium diisopropylamide (LDA)[4–6] in tetrahydrofuran (THF) at −78 °C. Coupling reaction of an anion (**2**) with α,β-unsaturated carbonyl compounds (**3a–d**) took place smoothly at −78 °C. Aldehydes (**3a**,**b**) afforded selectively the corresponding 1,2-adducts (**4a**,**b**) in high yields (>90%), while ketones (**3c**,**d**) gave the corresponding 1,2-adducts (**4c**,**d**) along with a considerable amount of 1,4-adducts.[7] 1,2-Adducts (**4a–d**) were dehydrated by the catalysis of *p*-toluenesulfonic acid (TsOH) in hot toluene. The desired dienes (**5a–d**) were produced as a stereoisomeric mixture of the *cis*,*trans*-isomer and *trans*,*trans*-isomer (*cis*,*trans*/*trans*,*trans* = 40/60 for **5a** and **5b**, 80/20 for **5d**), except the case of **4c**, which gave only *cis*,*trans*-isomer (*cis*,*trans*-**5c**,isolated in 83 % yield).[5,8] The structures of these dienes (**5**) were determined by ^{1}H NMR, ^{13}C NMR, NOE, IR, Mass, and HRMass spectral analysis[9] (Scheme 1).

As already described, lithiation of a methyl on 2,3-dimethylpyrazine (**1**) with butyllithium occurs to give an anion (**2**) effectively. Our initial interest was in whether the remained methyl of a pyrazine, produced by the first

Keywords: Pyrazine; 1,2,5-Oxadiazole; Intramolecular cyclization; 5*H*-Cycloheptapyrazine; 4*H*-Cyclohepta-1,2,5-oxadiazole.
* Corresponding author. Fax: +81-463-58-9684; e-mail: matsumo@chem.kanagawa-u.ac.jp

0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.03.123



Scheme 1.

homologation of 2,3-dimethylpyrazine (**1**), can undergo metal–proton exchange selectively with a lithium reagent such as LDA. First of all, we examined a lithiation of 2-[(4-methoxyphenyl)buta-1,3-dienyl]-3-methylpyrazine (**5a**). When *cis*,*trans*-**5a** (2.0 mmol) was treated with LDA in THF under N_2 atmosphere at −78 °C, a deep-violet-colored intermediary anion (**6a**) was produced immediately and cyclized spontaneously to give a 5*H*-cycloheptapyrazine (**7a**) in 90% yield after usual work-up and successive chromatographic purification on silica gel.[10] The structure of **7a** was determined by ^{1}H NMR, ^{13}C NMR, IR, Mass, and HRMass spectral analysis.[11] Similar treatment of the *cis*,*trans*-form of dienes (**5b–d**) with LDA gave the corresponding seven-membered ring products (**7b–d**) in 13–92% yields as shown in Table 1. A butadienylpyrazine (**5c**) afforded not only **7c** but also a small amount of its isomer (**8c**) (3%). It should be noted here for the LDA-induced reaction of **5** that little cyclization into five-membered ring products (**9**) occurred, though it should be formally possible as a concurrent pathway (vide infra) (Scheme 2).

A *trans*,*trans*-isomer of diene (**5**) is unable to undergo base-induced cyclization into a cycloheptene (**7** or **8**), if left alone, because an anionic methylene and a terminal carbon of a butadienyl unit are too remote from each other for the intramolecular cyclization. In fact, a *trans*,*trans*-isomer (*trans*,*trans*-**5a**) gave little of the seven-membered ring product and merely a large amount of intractable polymeric products when treated with LDA under the conditions described above (see Table 1). However, a potassium *tert*-butoxide/18-crown-6 ether complex, ($[K\subset(18C6)]^+\cdot t$-$BuO^-$), was found to be effective for the cyclization. When *trans*,*trans*-**5a** (2 mmol) was treated with 1.0 equiv of $[K\subset(18C6)]^+\cdot t$-$BuO^-$ in THF at room temperature for 1 h, a seven-membered ring products, **7a** and its isomer (**8a**), were produced in 17% and 37% yield, respectively. This result suggests that *trans*,*trans*-**5a** and/or its anionic form, *trans*,*trans*-**6a**, should isomerize into *cis*,*trans*-**5a** and/or an anion *cis*,*trans*-**6a** in $[K\subset(18C6)]^+\cdot t$-$BuO^-$/THF system prior to the cyclization.

A five-membered ring heteroaromatic compound, 3,4-dimethyl-1,2,5-oxadiazole, possesses a partial structure, —N=C(CH_3)–C(CH_3)=N—, which is formally an equivalent of diacetyl as in the case of 2,3-dimethylpyrazine (**1**).[12–14] A methyl of 3,4-dimethyl-1,2,5-oxadiazole has been reported also to undergo lithiation with butyllithium similarly to the case of 2,3-dimethylpyrazine.[15] Thus, we synthesized 3-(buta-1,3-dienyl)-4-methyl-1,2,5-oxadiazoles (**10a–d**) by the use of reaction sequences starting from α,β-unsaturated carbonyl compounds similarly to the case of butadienylpyrazines (**5**); *cis*,*trans*-isomer (*cis*,*trans*-**10**) and *trans*,*trans*-isomer (*trans*,*trans*-**10**) were produced concomitantly but separated easily from each other by column chromatography or crystallization. When *cis*,*trans*-isomers of butadienyloxadiazole (*cis*,*trans*-**10a–d**) were treated with LDA at −78 °C as in the case of *cis*,*trans*-**5**, the expected cyclization took place smoothly to afford the corresponding seven-membered ring products, 4*H*-cyclohepta-1,2,5-oxadiazoles, (**11a–d**) in 42–85% yield as shown in Table 1. Only *cis*,*trans*-**10a** gave an isomeric product (**12a**) as a by-product (8%) among *cis*,*trans*-**10** examined here. Furthermore, its *trans*,*trans*-isomer (*trans*,*trans*-**10a**) was found to undergo LDA-induced cyclization to give **11a** in moderate yield (32%) even at −78 °C. It is noteworthy that all butadienyl-1,2,5-oxadiazoles (**10**) examined here gave no detectable amount of five-membered ring products as in the case of pyrazines (**5**) (Scheme 3).

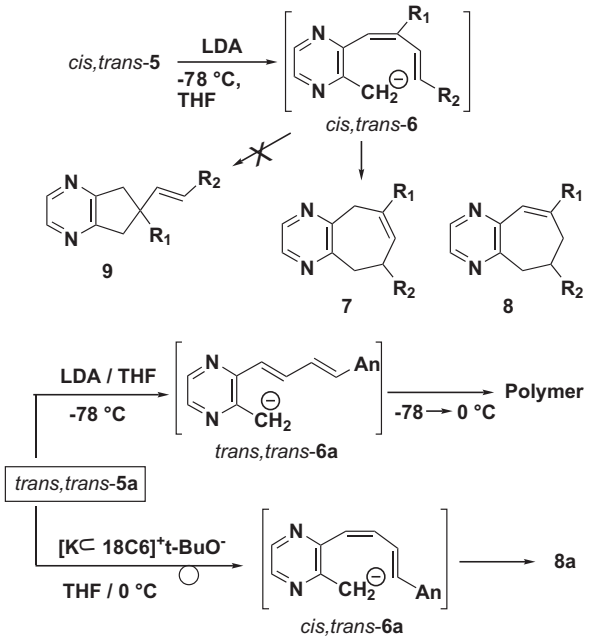
As described above, the LDA-induced reaction gave little of five-membered ring product(s) for neither

Table 1. Base-induced intramolecular cyclization of 2-(buta-1,3-dienyl)-3-methylpyrazine (**5**) and 3-(buta-1,3-dienyl)-4-methyl-1,2,5-oxadiazole (**10**)[a]

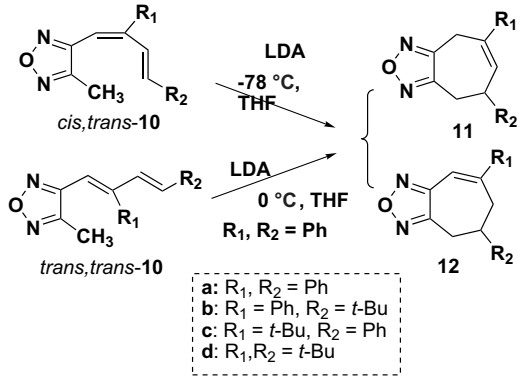
Diene	R_1	R_2	Conditions[b]	Product/%
cis,*trans*-**5a**	H	An	**A**	**7a**: 90
trans,*trans*-**5a**	H	An	**B**	Polymerized
trans,*trans*-**5a**	H	An	**C**	**7a**: 17, **8a**: 37
cis,*trans*-**5b**	H	Me	**A**	**7b**: 13
cis,*trans*-**5c**	Ph	Ph	**A**	**7c**: 92, **8c**: 3
cis,*trans*-**5d**	Ph	*t*-Bu	**A**	**7d**: 43
cis,*trans*-**10a**	Ph	Ph	**A**	**11a**: 80, **12a**: 8
trans,*trans*-**10a**	Ph	Ph	**A**	**11a**: 32
cis,*trans*-**10b**	Ph	*t*-Bu	**A**	**11b**: 85
cis,*trans*-**10c**	*t*-Bu	Ph	**A**	**11c**: 79
cis,*trans*-**10d**	*t*-Bu	*t*-Bu	**A**	**11d**: 42

[a] Unless otherwise stated, 2.0 mmol of substrate (**5** or **10**) was treated with 1.0–1.2 equiv of a base in THF (15 mL).

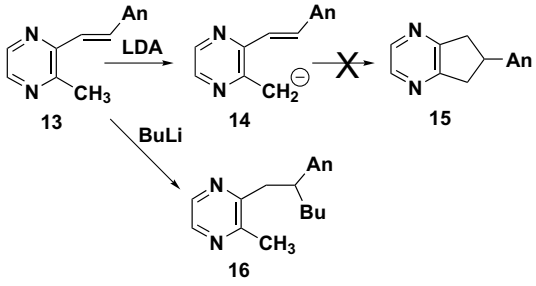
[b] **A**: LDA as a base, at −78 °C, for 1 h; **B**: LDA as a base, at −78 °C → 0 °C, for 1 h; **C**: a complex of *t*-BuOK with 18-crown-6 ether {$[K\subset(18C6)]^+ t$-BuO^-} as a base, at room temperature, for 30 min.



Scheme 2.



Scheme 3.



Scheme 4.

pyrazines (**5**) nor 1,2,5-oxadiazoles (**10**). Thus, 2-[2-(4-methoxyphenyl)ethenyl]-3-methylpyrazine (**13**) was synthesized as a rather simple model for examining a base-induced intramolecular cyclization into a five-membered ring product. On treatment with LDA, a styrylpyrazine (**13**) gave little of an expected cyclization product (**15**) and was still intact even at 0 °C. On the other hand, addition of butyllithium to a styrylpyrazine (**13**) took place to give a pyrazine (**16**) in 49% isolated yield, when **13** was treated with butyllithium in THF at −78 °C → room temperature for 1 h. These facts showed that a styryl moiety should be little activated toward an attack of a nucleophile for an anionic 2-methyl-3-styrylpyrazine (**14**), though a styryl moiety is active enough to allow a nucleophilic attack in a neutral form of **13**.[16] On similar treatment with butyllithium, both the *trans*,*trans*-isomer of butadienylpyrazine (*trans*,*trans*-**5a**) and its *cis*,*trans*-isomer (*cis*,*trans*-**5a**) gave only polymeric products (Scheme 4).

The above results suggest that LDA-induced intramolecular cyclization of butadienylmethylpyrazines (**5**) and their 1,2,5-oxadiazole analogs (**10**) is most likely regarded as an intramolecular electrocyclization of a C_7-8π-electron system rather than an intramolecular 1,6-addition[17,18] of a methyl carbanion to a butadienylimine moiety existing in the same molecule. This idea was supported by an AM1 MO calculation of an anion (*cis*,*trans* -**6a**), which suggested that a partial bond formation is already observed between an anionic methyl and an unsaturated carbon at the 4-position of a butadienyl moiety as illustrated in Figure 1.

The present results show a new type of intramolecular cyclization of C_7-8π-electron system comprised of a buta-1,3-dienyl, an anionic methyl, and two adjacent sp^2-carbons of the aromatic heterocycles, such as pyrazine and 1,2,5-oxadiazole, joining these two substituents. We are now investigating an effective transformation of seven-membered ring products **7** and **11** into the corresponding tropolones by a combination of dehydration of the seven-membered ring and successive hydrolysis of the heterocycles.

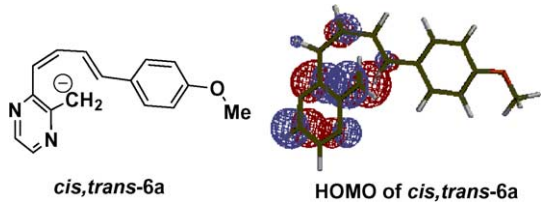


Figure 1.

References and notes

1. Treatment of polymethylpyrazines with an alkyllithium has been reported to lead not only to a desired lithiation of a methyl but to a concurrent alkylation of the pyrazine nuclei.[1,2] However, a product derived from substitution of a hydrogen on a heteroaromatic ring with a butyl group was little observed for the case presented here.
2. Rizzi, G. P. *J. Org. Chem.* **1968**, *33*, 1333–1337.
3. Rizzi, G. P. *J. Org. Chem.* **1974**, *39*, 3598–3599.
4. Houminer, Y. *J. Heterocycl. Chem.* **1981**, *18*, 15–17.
5. Houminer, Y. *J. Org. Chem.* **1980**, *45*, 999–1003.
6. Bassfield, R. L.; Houminer, Y. *J. Org. Chem.* **1983**, *48*, 2130–2133.
7. Ratios of 1,2-adduct versus 1,4-adduct were as follows: 52:48 for **3c**, and 71:29 for **3d**.
8. The present nomenclature, '*cis*,*trans*' or '*trans*,*trans*' is made to emphasize stereochemistry of a butadienyl side chain. Dienes (**5d**) were produced in rather poor yield along with a considerable amount of the starting ketone (**3d**), which might be produced by retro-aldol type reaction. A certain alcohol such as **4** has been reported to cause retro-aldol type reaction giving a methylpyrazine and the corresponding carbonyl through intramolecular hydrogen bonding of an alcoholic proton to a nitrogen of the pyrazine ring.[5]
9. Selected data for *cis*,*trans*-**5a**: yellow needles melted at 76.9–78.0 °C (from MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.60 (s, 3H), 3.82 (s, 3H), 6.43 (d, $J = 11.5$ Hz, 1H), 6.66 (dd, $J = 11.5$, and 11.2 Hz, 1H), 6.76 (d, $J = 15.6$ Hz, 1H), 6.87 (d with fine coupling, $J = 8.8$ Hz, 2H), 7.42 (d with fine coupling, $J = 8.8$ Hz, 2H), 8.01 (ddd, $J = 15.6$, 11.2, and 0.9 Hz, 1H), 8.28 (d, $J = 2.5$ Hz, 1H), 8.47 (d, $J = 2.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 22.2, 55.3, 114.1, 121.8, 124.0, 128.4, 129.9, 136.7, 138.2, 140.9, 141.4, 151.2, 152.3, 159.8; IR (KBr) 3066, 3045, 3007, 2969, 2931, 2838, 1602, 1594, 1509 cm^{-1}; Mass (*m*/*z*, %) 252 (M^+, 46), 251 (24), 237 (9), 145 (100); HRMS (ESI) 253.1331, calcd for $C_{16}H_{17}N_2O$ ($M+H^+$) 253.1341; Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.27; H, 6.62; N, 11.05. Selected data for *trans*,*trans*-**5a**: yellow needles melted at 157.3–158.5 °C (from Hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 2.63 (s, 3H), 3.83 (s, 3H), 6.80 (d, $J = 14.9$ Hz, 1H), 6.81 (d, $J = 15.6$ Hz, 1H), 6.89 (d with fine coupling, $J = 8.7$ Hz, 2H), 6.92 (ddd, $J = 15.6$, 11.0, and 0.7 Hz, 1H), 7.42 (d with fine coupling, $J = 8.7$ Hz, 2H), 7.63 (dd, $J = 14.9$ and 11.0 Hz, 1H), 8.25 (d, $J = 2.5$ Hz, 1H), 8.35 (d, $J = 2.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.7, 55.3, 114.2, 125.0, 126.3, 128.1, 129.7, 136.4, 136.6, 141.4, 141.8, 149.6, 151.0, 159.8; IR (KBr) 3044, 2998, 2835, 1597, 1523, 1508 cm^{-1}; Mass (*m*/*z*, %) 252 (M^+, 57), 251 (33), 237 (8), 145 (100); HRMS (ESI) 253.1331, calcd for $C_{16}H_{17}N_2O$ ($M+H^+$) 253.1341; Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.31; H, 6.37; N, 11.05.
10. Typical procedure (synthesis of **7a** from **5a**): A solution of *cis*,*trans*-**5a** (511 mg, 2.0 mmol) in THF (10 mL) was added to a solution of LDA (2.4 mmol, prepared from BuLi and diisopropylamine) in THF (5 mL) drop by drop under N_2 atmosphere at −78 °C over 40 min and stirred for additional 20 min. After usual work-up, the crude product was chromatographed on silica gel, and eluted with CH_2Cl_2–AcOEt to give **7a** in 90% yield.
11. Selected data for *5H*-cycloheptapyrazine **(7a)**: pale yellow plates melted at 100.8–101.2 °C (from Hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.36 (dd, $J = 13.3$ and 4.1 Hz, 1H), 3.42 (dd, $J = 13.3$ and 9.6 Hz, 1H), 3.64 (dd with fine coupling, $J = 17.0$ and 6.9 Hz, 1H), 3.71–3.77 (m, 1H), 3.78 (s, 3H), 3.94 (d with fine coupling, $J = 17.0$ Hz, 1H), 5.64 (d with fine coupling, $J = 11.9$ Hz, 1H), 5.93–6.00 (m, 1H), 6.83 (d with fine coupling, $J = 8.7$ Hz, 2H), 7.08 (d with fine coupling, $J = 8.7$ Hz, 2H), 8.24 (d, $J = 2.7$ Hz, 1H), 8.26 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 35.2, 42.7, 43.2, 55.2, 113.9, 123.4, 128.6, 133.2, 136.1, 140.9, 141.8, 155.3, 156.7, 158.3; IR (KBr) 3052, 3021, 2963, 2918, 2864, 2836, 1609, 1512 cm^{-1}; Mass (*m*/*z*, %) 252 (M^+, 100), 251 (37), 237 (19), 145 (30), 144 (29), 134 (20), 131 (19), 121 (24), 108 (22); HRMS (ESI) 253.1335, calcd for $C_{16}H_{17}N_2O$ ($M+H^+$) 253.1341; Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.23; H, 6.42, N; 11.12.
12. A pyrazine ring has been known to open by treatment with hydroiodic acid or by treatment with hydroxide ion after its transformation into a quarternary pyrazinium salt, though such ring opening has not been examined thoroughly.[13] A few examples of ring-opening reaction have been reported also for 1,2,5-oxadiazoles.[14]
13. Tutin, F. *J. Chem. Soc.* **1910**, 2495.
14. Ponzio, G.; Bilietti, F. *Gazz. Chim. Ital.* **1933**, *63*, 159.
15. Boger, D. L.; Brotherton, C. E. *J. Heterocycl. Chem.* **1981**, *18*, 1247.
16. An addition of butyllithium to a solution of anion (**14**) in THF gave little products.
17. Addition of a carbanion to a penta-2,4-dien-1-one or a penta-2,4-dienoate has been known.[18]
18. *Additions to and Substitutions at C–C π-Bonds*; Semmelhack, M. F., Ed.; In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds. Pergamon: Oxford, 1995; p 6, p 187.