Different Behavior of the Reaction between 1,2-Diaza-1,3-butadienes and 1,2-Diamines under Solvent or Solvent-Free Conditions

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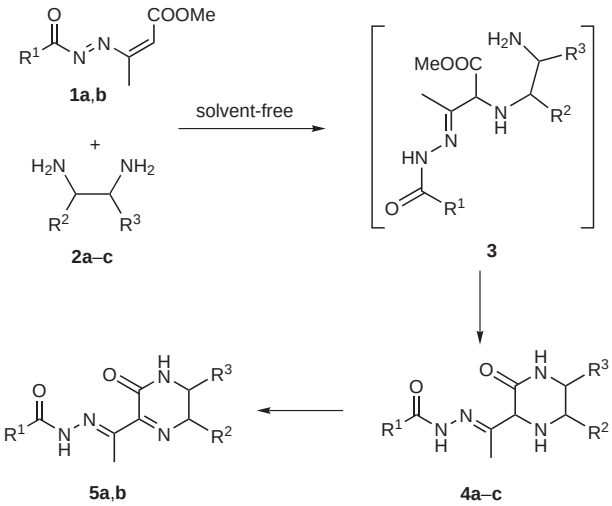
Abstract: New piperazinones are obtained in satisfactory yields by reaction of 1,2-diaza-1,3-butadienes with 1,2-diamines under solvent-free conditions. In polar solvents, the same reagents give rise to interesting dihydropyrazines and then to pyrazines by oxidation with PTAB or Pd/C.

Key word: Michael additions, regioselectivity, heterocyclic compounds, 1,2-diaza-1,3-butadienes, pyrazine derivatives

Pyrazines and piperazinones represent important classes of heterocycle rings as they occur in many pharmacologically active substances. The piperazinone ring has proven to be a valuable scaffold for the construction of biologically active molecules. Due in large part to their similarity with amino acids, piperazinones have proven to be useful tools for drug design and for evaluating interactions between natural ligands and macromolecules.[1] Pyrazines are useful for the treatment of obesity, psychiatric and neurological disorders.[2] Based on our previous experience on the chemistry of 1,2-diaza-1,3-butadienes,[3] we report herein a facile synthesis of pyrazine derivatives from these starting materials under mild conditions.

The reaction between 1,2-diaza-1,3-butadienes and 1,2-diamines **2a**–**c** has been carried out in MeCN or EtOH or under solvent-free conditions showing an unexpected and interesting different behaviour.



Scheme 1

1,2-Diaza-1,3-butadienes **1a**,**b** readily reacted under solvent-free conditions with 1,2-ethanediamine (**2a**), (±)-*trans*-1,2-diaminecyclohexane (**2b**), or (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine (**2c**) to give substituted piperazinones **4a**–**c** or **5a**,**b** (see Scheme 1 and Table 1). The first step of the reaction is the nucleophilic attack of an NH_2 group of compounds **2a**–**c** at the terminal C-atom of the azo-ene system of **1a**,**b** with the formation of 1,4-adducts **3**. The subsequent nucleophilic attack of the

Table 1 Results for the Synthesis of Piperazinones **4** and **5**[8]

Entry	1,2-Diaza-1,3-butadiene **1**	R^1	Diamine **2**	R^2	R^3	Product **4**	Product **5**	Yield (%)[a]	Temp (°C)
1	**1a**	NH_2	**2a**	H	H	**4a**		70	25
2	**1a**	NH_2	**2b**	$-(CH_2)_4-$			**5a**	42	45
3	**1a**	NH_2	**2c**	Ph	Ph	**4b**		65	90
4	**1b**	O*t*-Bu	**2a**	H	H	**4c**		88	25
5	**1b**	O*t*-Bu	**2b**	$-(CH_2)_4-$			**5b**	47	45

[a] Yield of pure isolated products based on 1,2-diaza-1,3-butadienes **1a**,**b**.

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Table 2 Results for the Synthesis of Piperazine Derivatives **6** and **7**[9,10]

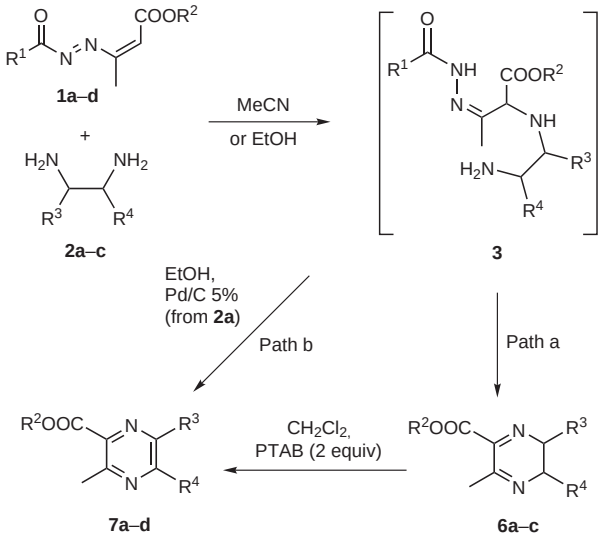
Entry	1,2-Diaza-1,3-butadiene **1**	R^1	R^2	Diamine **2**	R^3	R^4	Product **6**	Yield (%)[a]	Product **7**	Yield (%)[a]
1	**1a**	NH_2	Me	**2b**	$-(CH_2)_4-$		**6a**	49	**7a**	46
2	**1a**	NH_2	Me	**2c**	Ph	Ph	**6b**	68	**7b**	62
3	**1b**	O*t*-Bu	Me	**2b**	$-(CH_2)_4-$		**6a**	45	**7a**	43
4	**1c**	NH_2	Et	**2a**	H	H			**7d**	35
5	**1d**	O*t*-Bu	Et	**2a**	H	H			**7d**	32
6	**1d**	O*t*-Bu	Et	**2c**	Ph	Ph	**6c**	66	**7c**	60

[a] Yield of pure isolated products based on 1,2-diaza-1,3-butadienes **1a**–**d**.

second NH_2 group at the ester function with loss of an alcohol molecule produces compounds **4a**–**c** by ring closure.

In the case of the reaction between 1,2-diaza-1,3-butadienes **1a**,**b** and 1,2-diamine **2b**, a spontaneous oxidation takes place with the formation of pyrazine derivatives **5a**,**b** without the isolation of the relevant products **4**.

When the reaction between **1a**–**d** and **2a**–**c** was carried out in polar solvents such as MeCN or EtOH, a different behaviour was observed. After the formation of the same preliminary 1,4-adduct **3**, the cyclization process occurs by attack of the second NH_2 group at the C=N hydrazone carbon with successive loss of hydrazine molecule[4] (see Scheme 2 and Table 2). Then, an oxidative process affords pyrazines **6a**–**c**. The treatment of these compounds with the brominating agent phenytrimethylammonium tribromide (PTAB)[5] easily furnished pyrazines **7a**–**c** (Scheme 2, Path a). No products **4** or **5** were detected in the reaction mixture.



Scheme 2

The product **7d** has been synthesized by the treatment of intermediate **3** with Pd/C in EtOH under reflux[6] (Scheme 2, Path b). Complicated crude mixture likely due to degradation products has been observed for this reaction and only formation of slight traces of **4a**,**c** has been detected by chromatography. Therefore, only product **7d** was isolated.

In conclusion, this paper shows the different regioselectivity in the reaction between 1,2-diaza-1,3-butadienes and 1,2-diamines under solvent or solvent-free conditions. In this way it is possible to obtain interesting new pyrazines and piperazinones. Two known pyrazine compounds, methyl 3-methyl-5,6,7,8-tetrahydro-2-quinoxalinecarboxylate[7a] (**7a**) and ethyl 3-methyl-2-pyrazinecarboxylate[7b] (**7d**) used in the synthesis of biologically active molecules have been also synthesized. The advantage of this type of synthesis is the accessibility of the starting materials and the simplicity of the experimental procedures. Further explorations of the synthesis, reaction, and biological activity of these compounds are in progress.

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References

(1) (a) Dinsmore, C. J.; Beshore, D. C. *Org. Prep. Proced. Int.* **2002**, 367; and the references cited therein. (b) Zaleska, B.; Socha, R.; Karelus, M.; Szneler, E.; Grochowiski, J.; Serda, P. *J. Org. Chem.* **2003**, *68*, 2334.

(2) (a) In *Comprehensive Heterocyclic Chemistry*, Vol. 3; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**, 191–197. (b) In *Comprehensive Heterocyclic Chemistry*, Vol. 3; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**, 430–456. (c) In *The Chemistry of Heterocyclic Compounds*, Vol. 41; Weissberger, A.; Taylor, E. C., Eds.; Wiley Interscience: Chichester, **1982**, 8–10. (d) In *The Chemistry of Heterocyclic Compounds*, Vol. 33; Weissberger, A.; Taylor, E. C., Eds.; Wiley-Interscience: Chichester, **1978**, 888. (e) In *The Chemistry of Heterocyclic Compounds*, Vol. 33; Weissberger, A.; Taylor, E. C., Eds.; Wiley-Interscience: Chichester, **1978**, 1001–1004.

(3) (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Santeusanio, S. *ARKIVOC* **2002**, *xi*, 274; and the references cited therein. (b) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Santeusanio, S. *J. Org. Chem.* **2004**, *69*, 2686. (c) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Santeusanio, S. *Synlett* **2004**, 549.

(4) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusanio, S. *Helv. Chim. Acta* **2001**, *84*, 2379.

(5) (a) Wisweswariah, S.; Prakash, G.; Bhushan, V.; Chandrasekaran, S. *Synthesis* **1982**, 309. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Serra-Zanetti, F. *J. Heterocycl. Chem.* **1985**, *22*, 1341. (c) Attanasi, O. A.; Filippone, P.; Guerra, P.; Serra-Zanetti, F. *Synth. Commun.* **1987**, *17*, 555. (d) Attanasi, O. A.; Grossi, M.; Mei, A.; Serra-Zanetti, F. *Org. Prep. Proced. Int.* **1988**, *20*, 405. (e) Dauben, W. G.; Warshawsky, A. M. *Synth. Commun.* **1988**, *18*, 1323. (f) Jacques, J.; Marquet, A. *Org. Synth., Coll. Vol. VI*; Wiley and Sons: New York, **1988**, 175. (g) Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Foresti, E.; Mantellini, F. *J. Org. Chem.* **1998**, *63*, 9880. (h) Attanasi, O. A.; Filippone, P.; Guidi, B.; Perrulli, F. R.; Santeusanio, S. *Heterocycles* **1999**, *51*, 2423.

(6) (a) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 299. (b) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 668.

(7) (a) Gybaeck, H.; Johansson, M.; Minidis, A.; Nordvall, G.; Raboisson, P.; Wensbro, D. PCT Int. Appl. WO 2004069813, **2004**. (b) Merthes, M. P.; Lin, A. J. *J. Med. Chem.* **1970**, *13*, 77.

(8) **General Procedure for the Synthesis of Piperazinones 5a,b and 4a–c.**

1,2-Diaza-1,3-butadienes **1a**,**b** (0.5 mmol) were slowly added to a solution of 1,2-diamines **2a**–**c** (3 mmol) heated in an oil bath (for temperatures, see Table 1) with magnetic stirring. After the complete disappearance of 1,2-diaza-1,3-butadiene (monitored by silica gel TLC, 20 min) the crude reaction mixture was purified by chromatography on silica gel (elution mixture: EtOAc–MeOH, 90:10) for the products **5a**,**b** and **4b**. The excess of 1,2-diamine **2a** was evaporated under reduced pressure and the crude reaction mixture was purified by crystallization from EtOAc–MeOH for the products **4a**,**c**.

Data for *tert*-butyl 2-[1-(3-oxo-2-piperazinyl)ethylidene]-1-hydrazinecarboxylate (**4c**): white powder, mp 187–188 °C. IR (nujol): ν_{max} = 3229, 1723, 1698, 1659, 1541 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.43 (s, 9 H), 1.70 (s, 3 H), 2.76 (m, 1 H), 2,79 (br s, 1 H), 2.92 (m, 1 H), 3.04 (m, 1 H), 3.19 (m, 1 H), 3.80 (s, 1 H), 7.76 (s, 1 H), 9.47 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.55, 28.04, 41.21, 41.81, 66.07, 79.01, 150.82, 153.00, 167.82. MS: *m/z* (%) = 256 (2) [M^+], 239 (1), 200 (5), 183 (2), 139 (26), 126 (8), 110 (8), 98 (30), 83 (16), 69 (24), 57 (100). Anal. Calcd for $C_{11}H_{20}N_4O_3$: C, 51.55; H, 7.87; N, 21.86. Found: C, 51.64; H, 7.81; N, 21.79.

Data for *tert*-butyl 2-[1-(3-oxo-3,4,4a,5,6,7,8,8a-octahydro-2-quinoxalinyl)ethylidene]-1-hydrazinecarboxylate (**5b**): white powder, mp 195–197 °C. IR (nujol): ν_{max} = 3223, 1738, 1717, 1697, 1531 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.23 (m, 4 H), 1.43 (s, 9 H), 1.68 (m, 2 H), 1.87 (m, 1 H), 1.95 (s, 3 H), 2.17 (m, 1 H), 2.98 (m, 1 H), 3.06 (m, 1 H), 8.45 (s, 1 H), 9.87 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.34, 23.15, 24.65, 27.97, 29.99, 31.23, 53.46, 62.49, 79.65, 147.01, 152.72, 156.55, 161.53.
MS: *m/z* (%) = 307 (2) [M^+ – 1], 293 (2), 279 (2), 252 (2), 235 (2), 207 (4), 191 (4), 179 (10), 167 (10), 137 (10), 123 (10), 111 (16), 97 (28), 83 (30), 69 (44), 57 (100). Anal. Calcd for $C_{15}H_{24}N_4O_3$: C, 58.42; H, 7.84; N, 18.17. Found: C, 58.50; H, 7.79; N, 18.23.

(9) **General Procedure for the Synthesis of Substituted 5,6-Dihydropyrazines 6a–c and Substituted Pyrazines 7a–c.**

A stoichiometric amount of 1,2-diaza-1,3-butadiene **1a**,**b**,**d** (1.0 mmol) was slowly added to a solution of 1,2-diamines **2b**,**c** (1.0 mmol) in MeCN (50 mL). The reaction was allowed to stand at r.t. with magnetic stirring until complete disappearance of 1,2-diaza-1,3-butadiene (monitored by silica gel TLC, 1 h). The solvent was removed under reduced pressure and the products **6a–c** were purified by chromatography on silica, (elution mixture: cyclohexane–EtOAc, 30:70). In order to obtain the oxidized products **7a–c**, the crude mixture was dissolved with CH_2Cl_2 (150 mL) and PTAB (2 mmol) was slowly added. The crude reaction mixture was washed with H_2O (2 × 30 mL), the organic layer was dried over anhyd Na_2SO_4 and the solvent was evaporated under reduced pressure. The products **7a–c** were purified by chromatography on silica (elution mixture: cyclohexane–EtOAc, 60:40).

Data for methyl (5*R*,6*R*)-3-methyl-5,6-diphenyl-5,6-dihydro-2-pyrazinecarboxylate (**6b**): ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (d, ^5J = 2.4 Hz, 3 H), 3.95 (s, 3 H), 4.29 (dq, ^3J = 14.8 Hz, ^5J = 2.4 Hz, 1 H), 4.37 (d, ^3J = 14.8 Hz, 1 H), 6.95 (m, 4 H), 7.19 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.87, 53.05, 65.27, 66.13, 126.55, 126.85, 127.34, 127.40, 128.13, 128.21, 139.35, 140.03, 153.24, 155.58, 164.36. MS: *m/z* (%) = 306 (100) [M^+].

Data for methyl 3-methyl-5,6-diphenyl-2-pyrazinecarboxylate (**7b**) yellow powder, mp 102–104 °C. IR (nujol): ν_{max} = 1728, 1402, 1312 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.93 (s, 3 H), 4.01 (s, 3 H), 7.29 (m, 6 H), 7.48 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.73, 52.77, 128.21, 128.25, 128.64, 129.07, 129.58, 129.62, 137.59, 137.66, 139.40, 149.16, 151.91, 153.31, 165.87. MS: *m/z* (%) = 304 (100) [M^+]. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.89; H, 5.25; N, 9.14.

(10) **General Procedure for Synthesis of Ethyl 3-Methylpyrazine-2-carboxylate (7d).**

A solution of 1,2-diaza-1,3-butadienes **1c**,**d** (1 mmol) in EtOH (10 mL) was added dropwise to a magnetically stirred solution of 1,2-ethanediamine **2a** (1.0 mmol) in EtOH (50 mL). The reaction was allowed to stand at r.t. until complete disappearance of 1,2-diaza-1,3-butadiene (monitored by silica gel TLC, 1 h). The reaction was then treated with Pd/C (110 mg, 5%) with magnetic stirring and was refluxed for 14 h. The mixture was filtered and the solvent evaporated under reduced pressure. Product **7d** was purified by chromatography on silica gel (elution mixture: cyclohexane–EtOAc, 70:30).