An efficient oxidation of 2-pyrazolines and isoxazolines by bis-bromine-1,4-diazabicyclo[2.2.2]octane complex (DABCO-Br_2)

Davood Azarifar,* Kaveh Khosravi and Rahman-Ali Veisi

Faculty of Chemistry, Bu-Ali Sina University, Zip Code 65178, Hamedan, Iran
E-mail: azarifar@basu.ac.ir

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Abstract

An efficient and simple procedure has been developed for the oxidation of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles and -isoxazoles to their corresponding aromatic derivatives promoted by bis-bromine-1,4-diazabicyclo[2.2.2]octane complex (DABCO-Br_2) in acetic acid at room temperature. The products 2-pyrazoles and isoxazoles were produced in good to excellent 87-95 % and 78-95 % yields respectively.

Keywords: Bis-bromine-1,4-diazabicyclo[2.2.2]octane, DABCO-Br_2, isoxazoles, 2-pyrazoles, oxidation

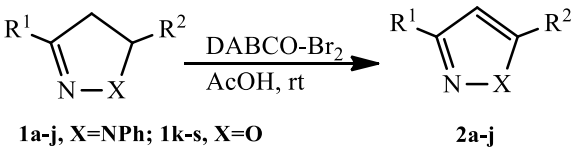
Introduction

Isoxazolines and pyrazolines have attracted much attention since they play important roles in synthetic organic over the years and are important bioactive compounds as anti-cancer,[1] anti-viral,[2] anti-inflammatory,[3] anti-diabetic,[4] anti-bacterial and antifungal agents.[5] In addition, a number of isoxazoles and pyrazoles exhibit fluorescence characteristics and can act as agrochemical herbicides, soil fungicides, pesticides and insecticides.[6] Furthermore, isoxazoles and pyrazoles are useful synthetic intermediates capable of undergoing various transformations and transition-metal catalyzed cross-coupling reactions, such as Heck, Stille, Suzuki, Sonogashira, and Negishi couplings.[7] Recently, transition-metal catalyzed coupling-cyclization reaction of functionalized allenes with organic halides for synthesis of pyrazoles has been reported.[8] These facts substantiate an obvious demand for development of new synthetic methods for isoxazoles and pyrazoles due to their importance both as synthetic intermediates[9] and as pharmacological targets.[10] Isoxazoles and 2-pyrazoles can be easily obtained respectively from oxidation of isoxazolines[11,12] and 2-pyrazolines.[10,13] Various efforts have been made previously in the oxidation of isoxazolines and 2-pyrazolines with a variety of reagents including Pd/C/acetic acid,[14] carbon-activated oxygen,[15] cobalt soap of fatty acids,[16] lead tetraacetate,[17]

mercury or lead oxide,[18] manganese dioxide,[19]potassium permanganate,[19,20] silver nitrate,[21] iodobenzene diacetate,[22] zirconium nitrate,[23] nickel peroxide,[24] cromite,[25] *N*-bromosuccinimide (NBS),[26] manganese triacetate,[27] sodium bicarbonate/dimethyl formamide,[28] 2,3-dichloro-5,6 dicyanobenzoquinone (DDQ),[29] sodium carbonate/methanol,[9] and tetrakispyridinenickel(II) dichromate.[30] However, many of these methods are subjected to certain drawbacks such as longer reaction times, low yields and toxicity due to the presence of some elements embodied in the reagents utilized. So still there is need of development of new catalysts which overcome all these drawbacks.

Results and Discussion

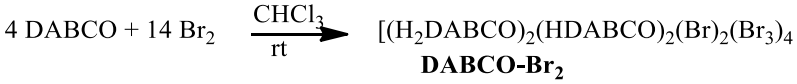
To broaden the scope of our ongoing research on developing more convenient and robust methods for oxidative aromatization of different heterocycles,[31-39] herein we wish to introduce bis-1,4-diazabicyclo[2.2.2]octane complex, (DABCO-bromine), in this letter as a new and efficient reagent for conversion of isoxazolines and 2-pyrazolines into their corresponding isoxazoles and 2-pyrazoles (Scheme 1**)**.



1a-j, X=NPh; 1k-s, X=O **2a-j**

Scheme 1

DABCO-bromine complex can be conveniently prepared from easily available and inexpensive 1,4-diazabicyclo[2.2.2]octane by its treatment with bromine/chloroform solution (Scheme 2). Previously this complex has been used by others in conversion of alcohols into carbonyl compounds,[40] desilylation of silyl ethers,[41] and also employed as a catalyst in the synthesis of *N*-arylphthalimides.[42]



Scheme 2

In this communication, DABCO-bromine complex has been found to efficiently catalyze the aromatization of 2-pyrazolines **1a-j** and isoxazolines **1k-s** in acetic acid at room temperature within few minutes to afford the corresponding 2-pyrazoles **2a-j** and isoxazoles **2k-s** respectively in 87-95 % and 78-95 % yields (Table 1). As shown in the suggested mechanism (Scheme 3), it is likely that DABCO-bromine complex initially acts as a source for Br^+ which is transferred to nitrogen atom in the azoline ring to convert it into an azolinium cation. The positively charged azolinium ion thus formed is now activated to undergo hydrogen loss successively in two steps to provide the corresponding azole.

Conclusion

In conclusion, the present work offers a mild and simple procedure for oxidative aromatization of isoxazolines and 2-pyrazolines promoted by DABCO-bromine complex as a low cost and non-toxic reagent in AcOH at room temperature. Other advantages of this method are shorter reaction times, high yields of the products, and use of AcOH as a low cost and non-toxic solvent in the oxidation reactions.

Table 1. Oxidative aromatization of 2-pyrazolines **1a-j** and isoxazolines **1k-s** to the corresponding pyrazoles **2a-j** and isoxazoles **2k-s** with DABCO-bromine complex in acetic acid at rt.

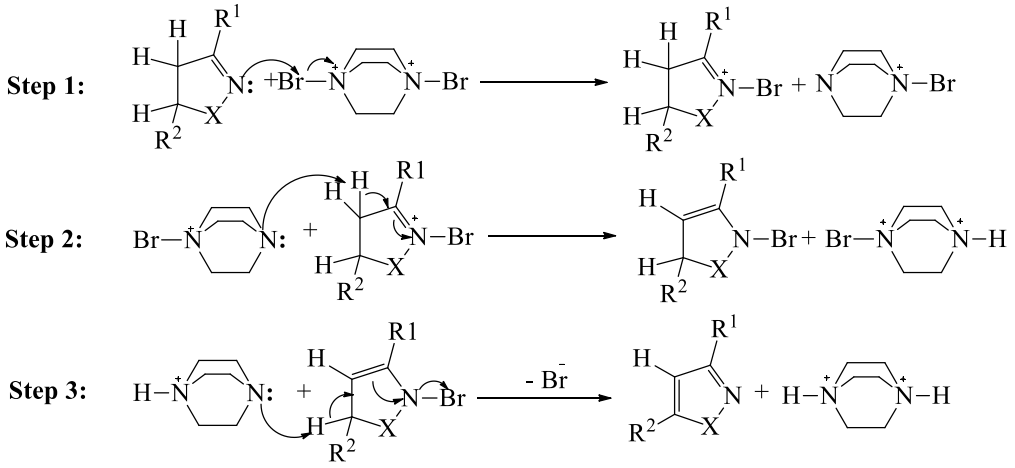
Substrate	Product	X	R^1	R^2	Time (h)	Yield[a] (%)	mp (˚C) Found	mp (˚C) Reported
1a	**2a**	NPh	Ph	Ph	2.5	92	137-139	139-140 [33c]
1b	**2b**	NPh	Ph	4-ClC_6H_4	3	94	110-112	114-115 [43]
1c	**2c**	NPh	Ph	3-ClC_6H_4	3	94	95-97	93-95 [33c]
1d	**2d**	NPh	4-$MeOC_6H_4$	Ph	4	90	75-77	77-79 [33c]
1e	**2e**	NPh	2-Naphthyl	4-ClC_6H_4	3.5	87	130-132	130-133 [33a]
1f	**2f**	NPh	2-Naphthyl	2-MeC_6H_4	3.4	88	144-146	148-150 [33c]
1g	**2g**	NPh	2-Naphthyl	2-ClC_6H_4	3.5	89	71-73	67-70 [33c]
1h	**2h**	NPh	2-Thienyl	4-ClC_6H_4	3	95	132-134	136-138 [37]
1i	**2i**	NPh	3-Thienyl	4-ClC_6H_4	3	95	144-146	145-148 [37]
1j	**2j**	NPh	3-Thienyl	4-$Me_2NC_6H_4$	3.5	92	118-120	120-123 [37]
1k	**2k**	O	1-Naphthyl	2-ClC_6H_4	5.5	95	65-67	64-65 [38]
1l	**2l**	O	2-Naphthyl	2-ClC_6H_4	5	90	92-94	94-95 [38]
1m	**2m**	O	2-Naphthyl	2-Thienyl	5.2	87	117-119	118-120 [38]
1n	**2n**	O	2-Naphthyl	4-$MeOC_6H_4$	5.4	82	105-107	107-109 [38]

1o	**2o**	O	2-Naphthyl	3-ClC_6H_4	5	78	92-93	90-92 [38]
1p	**2p**	O	2-Naphthyl	2-Styryl	5	95	164-166	165-167 [38]
1q	**2q**	O	2-Thienyl	4-ClC_6H_4	5.5	90	191-193	192-194 [38]

Table 1. Continued

Substrate	Product	X	R^1	R^2	Time (h)	Yield[a] (%)	mp (˚C) Found	mp (˚C) Reported
1r	**2r**	O	2- Furyl	4-ClC6H4	5.8	82	122-124	124-125 38
1s	**2s**	O	2-Pyrrolyl	4-ClC_6H_4	5.3	95	186-187	185-187 [38]

[a] Refer to isolated yields.



Scheme 3. X = NPh, O .

Experimental Section

General. All the reagents and chemicals used were of analytical grade and were purchased from Merk Chemical Co. Melting points were determined in open capillary tubes in a Stuart SMP_3 apparatus and uncorrected. Nuclear magnetic resonance spectra were recorded on a JEOL FX 90Q spectrometer using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Perkin Elmer GX FT IR spectrometer (KBr pellets). 2-Pyrazolines and isoxazolines used in this work were all prepared as reported.[10-13] 2-Pyrazoles and isoxazoles were characterized on the basis of their melting points and IR, ^{1}H NMR, and ^{13}C NMR spectral analysis and compared with those reported.[33,37,38,43] DABCO-Bromine complex was prepared according to the literature,[40] as described below.

Preparation of DABCO-Br2. To a magnetically stirred solution of 1,4-diazabicyclo [2.2.2]octane (DABCO) (6.72 g, 60 mmoles) in chloroform (100 mL) was added drop wise a

solution of bromine (20.0 g, 125 mmoles) in chloroform (100 mL) at rt. The resulting mixture was let to stir for a further one hour. Upon the removal of the excess bromine by evaporation under reduced pressure a yellow solid was precipitated, which was filtered to leave almost a pure yellow product, yield 98%, mp: 160-165 ˚C (decomp).

Oxidation of 2-pyrazolines (1a-j) and isoxazolines (1k-s) with DABCO-bromine complex; General Procedure

To a magnetically stirred suspension of DABCO-bromine complex (0.32g , 0.2 mmol) in glacial acetic acid (3 mL), was added 2-pyrazoline **1a-j** or isoxazoline **1k-s** (0.1 mmol). The resulting reaction mixture was stirred at rt for an appropriate time (Table 1). After the complete conversion of the substrate in 2.5-5.8 h. as monitored by TLC using acetone/n-hexane (4:1), the reaction mixture was quenched with aqueous sodium bicarbonate solution (5%) and extracted with ethyl ether (10 mL). The organic layer was then dried over anhydrous sodium sulphate and concentrated to leave the crude solids **2a-s** in 78-95 % yield (Table 1). The products were further purified by recrystallization from ethanol (96%).

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References

1. (a) Shin, K. D.; Lee, M.-Y.; Shin, D.-S.; Lee, S.; Son, K.-H.; Koh, S.; Paik, Y.-K.; Kwon, B.-M.; Han, D. C. *J. Biol. Chem*. **2005**, *280*, 41439. (b) Amer, F. A.; Hammouda, M.; El-Ahl, A. A. S.; Abdol-Wahab, B. F. *J. Chin. Chem. Soc*. **2007**, *54*, 1543. (c) Abdolhamid, A. O.; El-Ghandour, A. H.; El-Reedy, A. A. M. *J. Chin. Chem. Soc*. **2008**, *55*, 406.
2. Sechi, M.; Sannia, L.; Carta, F.; Palomba, M.; Dallocchio, R.; Dessi, A.; Derudas, M.; Zawahir, Z.; Neamati, N. *Antiviral Chem. Chemother*. **2005**, *16*, 41.
3. Rapposelli, S.; Lapucci, A.; Minutolo, F.; Orlandini, E.; Ortore, G.; Pinza, M.; Balsamo, A. *Farmaco* **2004**, *59*, 25.
4. Cottineau, B.; Toto, P.; Marot, C.; Pipaud, A.; Chenault, J. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2105.
5. (a) Cali, P.; Naerum, L.; Mukhija, S.; Hjelmencrantz, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5997. (b) Shinde, S.; Jadhav, W.; Pawar, R.; Bhusare, S. *J. Chin. Chem. Soc*. **2004**, *51*, 775. (c) Al-Omran, F.; El-Khair, A. A. *J. Heterocycl. Chem.* **2004**, *41*, 327.
6. (a) Li, Y.; Zhang, H.-Q.; Liu, J.; Yang, X.-P.; Liu, Z.-J. *J. Agric. Food Chem.* **2006**, *54*, 3737. (b) Raslan, M. A.; AbdEl-Aal, R. M.; Hassan, M. E.; Ahmed, N. A.; Sadek, K. U. *J.*

Chin. Chem. Soc. **2001**, *48*, 91.
7. Garvin, G. M.; Jackson, J. L.; McQuiston, J. M.; Ricks, M. J.; Thibault, T. D.; Turner, J. A.; VanHeertum, J. C.; Weimer, M. R. *Pest Manage. Sci.* **2002**, *58*, 1175.
8. (a) Ma, S. *Acc. Chem. Res*. **2003**, *36*, 701. (b) Cheng, X.; Ma, S. *Chem. Commun*. **2009**, 4263. (c) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc*. **2006**, *128*, 74.
9. Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283.
10. Nunno, L. D.; Scilimati, A.; Vitale, P. *Tetrahedron* **2002**, *58*, 2659.
11. (a) Azarifar, D.; Shaebanzadeh, M. *Molecules* **2002**, *7*, 885. (b) Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd ed.; John Willey & Sons: New York, NY, 1992, p. 294. (c) Shang, Y. J.; Wang, Y. G. *Tetrahedron Lett*. **2002**, *43*, 2247. (d) Kozikowski, A. P. *Acc. Chem. Res*. **1984**, *17*, 410. (e) Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. *Tetrahedron Lett*. **1998**, *39*, 2447.
12. (a) Parham, W. E.; Dooley, J. F. *J. Am. Chem. Soc*. **1967**, *89*, 985. (b) Bhatnagar, I.; George, M. V. *Tetrahedron* **1968**, *24*, 1293.
13. (a) Kedar, R. M.; Vidhale, N. N.; Chincholkar, M. M. *Orient. J. Chem*. **1997**, 143. (b) Sammour, A. B.; Blakasaby, M. *J. Chem. U. A. R.* **1969**, *12*, 1. (c) Aziz, G.; Nosseir, M. H.; Doss, N. L.; Rizk, A. S. *Ind. J. Chem*. **1967**, *14B*, 286. (d) Blatt, A. H. *J. Am. Chem. Soc*. **1949**, *71*, 1861. (e) Khalil, Z. H.; Yanni, A. S.; Abdel-Hafez, A. A.; Khalaf, A. A. *J. Ind. Chem. Soc*. **1988**, *64*, 42.
14. (a) Azarifar, D.; Ghasemnejad, H. *Molecule* **2003**, *8*, 642. (b) Azarifar, D.; Maleki, B. *J. Heterocycl. Chem*. **2005**, *42*, 157.
15. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett*. **2002**, *4*, 3955.
16. (a) Hayashi, M.; Kawashita, Y. *Lett. Org. Lett.* **2006**, *3*, 571. (b) Kawashita, Y.; Ueba, C.; Hayashi, M. *Tetrahedron Lett*. **2006**, *47*, 4232. (c) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, 1015. (d) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett*. **2003**, *5*, 3713.
17. Shah, J. N.; Shah, C. K. *J. Org. Chem*. **1978**, *43*, 1266.
18. Goldstone, W. A. F.; Norman, R. O. C. *J. Chem. Soc*., *Chem. Commun*. **1966**, 1537.
19. Auwers, K.; Heimke, P. *Liebigs Ann*. **1927**, *458*, 186.
20. Smith, L. I.; Howard, K. L. *J. Am. Chem. Soc*. **1943**, *65*, 159.
21. Kochetkov, N. K.; Sokolov, S. D. "*Advances in Heterocyclic Chemistry*", Academic Press: New York, **1965**, p. 420.
22. Dodwadmath, R. P.; Wheeler, T. S. *Proc. Ind. Acad. Sci*. **1936**, *2A*, 438.
23. Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. *Synth. Commun*. **1997**, *27*, 2683.
24. Sabitha, G.; Kumar Reddy, G. S. K.; Reddy, C. S.; Fatima, N.; Yadav, J. S. *Synthesis* **2003**, 1267.
25. Easton, C. J.; Heath, G. A.; Merricc, C.; Hughes, M. *J. Chem. Soc*. **2001**, *1*, 1168.
26. Blatt, A. H. *J. Am. Chem. Soc*. **1949**, *71*, 1861.

27. (a) Simoni, D.; Robert, M.; Invidiata, F. P.; Rondanin, R.; Malagutti, C.; Mazzali, A.; Ross, M.; Grimaudo, S.; Capone, F.; Dusoncher, L. *J. Med. Chem.* **2001**, *44*, 2308. (b) Walter, R.; Rienhard, L. *Chem. Ber.* **1969**, *102*, 378.
28. Chuang, C. P.; Jiang, M. C. *Tetrahedron* **1999**, *45*, 11229.
29. Chang, R. K.; Kim, K. *Tetrahedron Lett.* **2000**, *41*, 8499.
30. Bianchi, L.; Dellerba, C.; Grasparrini, F.; Novi, M.; Tavani, C. *Arkivoc* **2002**, (*xi)*, 142.
31. Wang, B.; He, T.; Li, C.; Hu, H. *Chin. J. Org. Chem.* **2003**, *23*, 794.
32. (a) Azarifar, D.; Zolfigol, M. A.; Maleki, B. *Bull. Korean Chem. Soc.* **2004**, *25*, 23. (b) Azarifar, D.; Zolfigol, M. A.; Maleki, B. *Synthesis* **2004**, 1744.
33. (a) Zolfigol, M. A.; Azarifar, D.; Maleki, B. *Tetrahedron Lett.* **2004**, *45*, 2181. (b) Azarifar, D.; Maleki, B. *J. Chin. Chem. Soc*. **2004**, *52*, 1215. (c) Azarifar, D.; Maleki, B. *Synth. Commun*. **2005**, *36*, 2581.
34. (a) Ghorbani-Vaghei, R.; Azarifar, D.; Maleki, B. *Bull. Korean Chem. Soc.* **2004**, *25*, 953. (b) Ghorbani-Vaghei, R.; Azarifar, D.; Khazaei, A.; Maleki, B. *Phosphorus Sulfur and Silicon* **2004**, *179*, 1877. (c) Ghorbani-Vaghei, R.; Azarifar, D.; Maleki, B. *J. Chin. Chem. Soc*. **2004**, *51*, 1373. (d) Azarifar, D.; Ghorbani-Vaghei, R.; Nadimi, E.; Maleki, B. *Mendeleev Commun*. **2006**, 329.
35. Azarifar, D.; Maleki, B. *Heterocycles* **2005**, *65*, 865.
36. Zolfigol, M. A.; Azarifar, D.; Mohammadpour-Baltork, I.; Mallakpour, S.; Forghaniha, A.; Maleki, B.; Abdollahi-Alibeik, M. *Tetrahedron Lett.* **2006**, *47*, 833.
37. Azarifar, D.; Gharshasebi, A. *Heterocycles* **2006**, *68*, 1209.
38. Azarifar, D.; Maleki, B.; Mohammadi, K. *Heterocycles* **2007**, *71*, 683.
39. Azarifar, D.; Khosravi, K. *J. Chin. Chem. Soc*. **2009**, *56*, 43.
40. Heravi, M. M.; Derikvand, F.; Ghassemzadeh, M.; Nemuller, B. *Tetrahedron Lett.* **2005,** *46*, 6243.
41. Sharafi, T.; Heravi, M. M. *Phosphorus Sulfur and Silicon* **2004**, *179*, 2437.
42. Heravi, M. M.; Hekmat-Shoar, R.; Pedram, L. *J. Mol. Catal. A: Chem*. **2005**, *232*, 89.
43. Han, B.; Liu, Z.; Liu, Q.; Yang, L.; Liu, Z.-L.; Yu, W. *Tetrahedron* **2006**, *62*, 2492.