1,3-Dibromo-5,5-dimethylhydantoin as a Novel Oxidizing Agent for the Oxidation of 1,3,5-Trisubstituted Pyrazolines under Both Heterogeneous and Solvent-free Conditions

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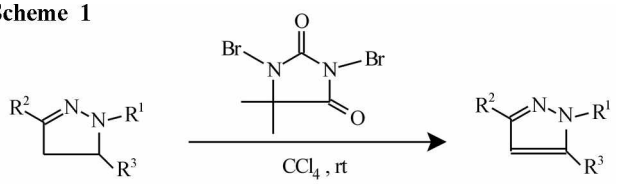
Five-membered heterocyclic compounds are stable aromatic compounds and have been used commercially as pharmaceuticals, pesticides, and dyestuffs. These compounds are also important constituents that often exist in biologically active natural products and synthetic compounds of medicinal interest.[1,2] Conversion of 1,3,5-trisubstituted pyrazolines with sensitive functional groups to their corresponding pyrazoles derivatives is a tricky step. Although a variety of reagents such as Pd/C/acetic acid,[3] acid cobalt soap of fatty acids,[4] lead tetraacetate,[5] mercury oxide,[6] manganese dioxide,[7] potassium permangenate,[8] silver nitrate,[9] iodobenzene diacetate,[10] zirconium nitrate[11] are capable of affecting the pyrazolines oxidation, this transformation remains capricious because these compounds are very sensitive to the oxidizing agents and reaction conditions. Moreover, most of the reported reagents produce some by-products, which either destroy, or are difficult to remove from the sensitive pyrazoles.[4] Another major drawback to the older procedures is their use of reagents which are either highly toxic or produce serious disposal problems (or both).

Our goal, in undertaking this line of work, was three-fold: a) to overcome the limitations and drawbacks of the reported methods such as tedious work-up, acidic media,[3] and safety problems (presence of toxic transition metal cations such as Co(II),[4] Pb(IV),[5] Hg(II),[6] Mn(IV and VII),[7,8] Ag(I),[9] Zr(IV)[11] within molecular structure of the reagents); (b) solvent-free organic synthesis seems to be a highly useful technique, especially for industry and it has many advantages: reduced pollution, low costs, and simplicity in process and handling (these factors are especially important in industry).[12-14] (c) moreover, to develop a high-yielding synthesis of pyrazoles by using a novel commercially available reagent. Therefore, we were interested to find a heterogeneous system for pyrazoline oxidation. In continuation of our studies in this regard,[1] we have found that DBH a cheap commercially available reagent, which recently used as an excellent reagent for analytical purposes,[15-20] has found little application in organic chemistry.[21-27] Therefore, we wish to report a simple, cheap and convenient method for the effective conversion of 1,3,5-trisubstituted pyrazolines (**1**) to their corresponding pyrazoles (**2**) by using DBH both under heterogeneous and also solvent free-conditions (Scheme 1).

Scheme 1



1 **2**

Substrate	Product	R^1	R^2	R^3
1a	**2a**	Ph	2-Naphthyl	2-$CH_3C_6H_4$
1b	**2b**	Ph	2-Naphthyl	Ph
1c	**2c**	Ph	Ph	Ph
1d	**2d**	Ph	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$
1e	**2e**	Ph	3-$CH_3C_6H_4$	2-ClC_6H_4
1f	**2f**	Ph	4-$CH_3OC_6H_4$	3-$CH_3C_6H_4$
1g	**2g**	Ph	4-$CH_3OC_6H_4$	2-$CH_3C_6H_4$
1h	**2h**	Ph	4-$CH_3OC_6H_4$	Ph
1i	**2i**	Ph	4-$CH_3OC_6H_4$	4-ClC_6H_4
1j	**2j**	Ph	3-$CH_3C_6H_4$	4-ClC_6H_4
1k	**2k**	Ph	2-Naphthyl	3-$CH_3C_6H_4$
1l	**2l**	Ph	2-Naphthyl	4-ClC_6H_4
1m	**2m**	Ph	2-Naphthyl	2-ClC_6H_4
1n	**2n**	Ph	3-$CH_3C_6H_4$	4-$(CH_3)_2NC_6H_4$
1o	**2o**	Ph	2-$CH_3C_6H_4$	4-$(CH_3)_2NC_6H_4$
1p	**2p**	Ph	4-$CH_3OC_6H_4$	2-ClC_6H_4
1q	**2q**	$COCH_3$	2-Naphthyl	2-$CH_3C_6H_4$
1r	**2r**	$COCH_3$	2-Naphthyl	3-$CH_3C_6H_4$
1s	**2s**	$COCH_3$	3-$CH_3C_6H_4$	2-ClC_6H_4
1t	**2t**	$COCH_3$	2-$CH_3C_6H_4$	2-ClC_6H_4
1u	**2u**	CH_3CH_2	Ph	Ph

Different kinds of 1,3,5-trisubstituted pyrazolines were subjected to oxidation reaction in the presence of DBH in CCl_4 (Scheme 1) or solvent-free conditions. The oxidation reactions were performed under mild conditions at room temperature with good yields. The 1,3,5-trisubstituted pyrazoles (**2**) can be obtained by simple filtration and evaporation of the solvent.[28-30] The results and reaction conditions are given in the Table. N-Bromosuccinimide was also used as oxidizing agent under same condition (Entries 2 and 4).

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Table 1. Oxidation of 1,3,5-trisubstituted pyrazolines (**1**) to their corresponding pyrazoles (**2**) with 1,3-Dibromo-5,5-dimethylhydantoin (DBH) or *N*-bromosuccinimide (NBS) both in carbon tetrachloride (**I**) and solvent-free conditions (**II**) at room temperature

Entry	Substrate	Product[a]	Reagent/Substrate[b]		Time (h)	Yield[c] (%)
			I	II	**I** (**II**)	**I** (**II**)
1	**1a**	**2a**	1	2.5	0.3 (1)	94 (85)
2	**1a**	**2a**	1.25[d]	4[d]	0.3[d] (1)[d]	80[d] (72)[d]
3	**1b**	**2b**	1	2.25	0.3 (1.25)	98 (90)
4	**1b**	**2b**	1.25[d]	4[d]	0.3[d] (1.25)[d]	85[d] (75)[d]
5	**1c**	**2c**	1	2.25	0.5 (1.25)	90 (83)
6	**1d**	**2d**	1.5	3.75	0.5 (1.5)	93 (87)
7	**1e**	**2e**	2.25	3.5	0.3 (0.75)	98 (90)
8	**1f**	**2f**	1.75	3	0.5 (1)	95 (90)
9	**1g**	**2g**	1.75	3.5	0.5 (1)	90 (85)
10	**1h**	**2h**	2	3.5	0.3 (1)	70 (63)
11	**1i**	**2i**	1.25	3.75	0.5 (1.5)	81 (76)
12	**1j**	**2j**	2.25	4	0.75 (1.5)	96 (92)
13	**1k**	**2k**	2.25	3.75	0.75 (1.25)	98 (91)
14	**1l**	**2l**	2.5	3.75	0.5 (1.25)	92 (87)
15	**1m**	**2m**	2.25	3.5	0.5 (1)	85 (74)
16	**1n**	**2n**	2	3.25	0.3 (0.75)	88 (76)
17	**1o**	**2o**	2	3	0.3 (0.75)	92 (85)
18	**1p**	**2p**	2	3.5	0.3 (1)	90 (82)
19	**1q**	**2q**	3.5	14	1 (2.25)	94 (86)[e]
20	**1r**	**2r**	3.5	15	0.75 (3)	92 (89)[e]
21	**1s**	**2s**	4.25	18	1.75 (4.5)	90 (72)[e]
22	**1t**	**2t**	4	15	1.75 (2.5)	93 (80)[e]
23	**1u**	**2u**	1	2	0.15 (0.3)	90 (80)

[a]All of the isolated products are known compounds and their spectra and physical data have been reported in the literature.[2-11] [b]Molar ratio of 1,3-Dibromo-5,5-dimethylhydntoin (DBH) in CCl_4 (**I**) mmol and under solvent free conditions (**II**) mmol. [c]Isolated yields. [d]*N*-Bromosuccinimide (NBS) was used as oxidizing agent. [e]These reactions were occurred at 80 °C under solvent free conditions.

In conclusion, practical and efficient oxidations of 1,3,5-trisubstituted pyrazolines have been achieved by the new methodology described. Thus this reagent could be used for the oxidation of a wide variety of pyrazolines derivatives under safe condition.

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References

1. Azarifar, D.; Shaebanzadeh, M. *Molecules* **2002**, *7*, 885.
2. Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd Ed; John Willey & Sons, Inc.: New York, 1992; p 294.
3. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955.
4. Shah, J. N.; Shah, C. K. *J. Org. Chem.* **1978**, *43*, 1266.
5. Goldstone, W. A. F.; Norman, R. O. C. *J. Chem. Soc. Chem. Commun.* **1966**, 1536.
6. Auwers, K.; Heimke, P. *Liebigs Ann.* **1927**, *458*, 186.
7. Bhatnagar, I.; George, M. V. *Tetrahedron* **1968**, *24*, 1293.
8. Smith, L. I.; Howard, K. L. *J. Am. Chem. Soc.* **1943**, *65*, 159.
9. Dodwadmath, R. P.; Wheeler, T. S. *Proc. Ind. Acad. Sci.* **1935**, *2A*, 438.
10. Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. *Synth. Commun.* **1997**, *27*, 2683.
11. Sabitha, G.; Kumar Reddy, G. S. K.; Reddy, Ch. S.; Fatima, N.; Yadav, J. S. *Synthesis* **2003**, 1267.
12. Varma, R. S. *Green Chem.* **1999**, *1*, 43.
13. Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
14. Krehnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61.
15. Hilp, M.; Senjuk, S. *J. Pharm. Biomed. Anal.* **2001**, *25*, 363.
16. Hilp, M. *Pharmazie* **2001**, *56*, 777.
17. Hilp, M. *Pharmazie* **2002**, *57*, 45.
18. Hilp, M. *Pharmazie* **2002**, *57*, 316.
19. Hilp, M. *J. Pharm. Biomed. Anal.* **2002**, *28*, 303.
20. Hilp, M. *J. Pharm. Biomed. Anal.* **2002**, *28*, 337.
21. Walter, T. R.; Zajac, W. W.; Woods, J. M. *J. Org. Chem.* **1991**, *56*, 1316.
22. Uchibori, Y.; Umeno, M.; Seto, H.; Yoshioka, I. *Chem. Lett.* **1993**, *4*, 673.
23. Shimizu, M.; Nakahara, Y.; Yoshioka, H. *J. Chem. Soc. Chem. Commun.* **1989**, *24*, 1881.
24. Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986**, *51*, 3508.
25. Shimizu, M.; Nakahara, Y.; Yoshioka, H. *J. Fluorine Chem.* **1999**, *97*, 57.
26. Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1997**, *38*, 4415.
27. Furuta, S.; Hiyama, T. *Tetrahedron Lett.* **1996**, *37*, 7983.
28. Chemicals were purchased from Fluka, Merck, Riedel-dehaen AG and Aldrich chemical companies. Yields refer to isolated pure products. The oxidation products were characterized by comparison of their spectral (IR, and ^{1}H-NMR.) and physical data with the authentic samples.[3-11] All 1,3,5-trisubstituted pyrazolines were synthesized according to our previously reported procedure.[1]
29. General procedure for oxidation of pyrazoline in solution: A suspension of DBH (The molar ratio of DBH to the substrate **1** were given in the Table), pyrazoline **1** (2 mmol) and CCl_4 (10 mL) was stirred vigorously magnetically at room temperature. The progress of the reaction was followed by TLC. Reactions were completed after 0.3-4.5 hrs (Table). After the reaction was completed, K_2CO_3 (1 g) added to the reaction mixture, and the resulting mixture was stirred vigorously magnetically for 0.5 h. Then solid materials were removed by filtration and washing with CCl_4 (10 mL). The solvent was evaporated and the pyrazoles (**2**) were obtained (Table). If further purification is needed, flash chromatography on silica gel [eluent: *n*-hexane : acetone (10 : 1)] to give highly pure **2**.
30. Oxidation of pyrazoline (**1c**) to pyrazole (**2c**) with DBH under solventfree condition. A typical procedure. A mixture of compound **1c** (596 g, 2.0 mmol) and DBH (1.429 g, 5 mmol) was shaken at room temperature for 1.25 hour. After the reaction was completed, K_2CO_3 (1 g) was added to the reaction mixture, and shaken for 0.5 h. Dichloromethane (20 mL) was added to the resulting mixture then filtered. Dichloromethane was removed. The yield was 0.491 g (83%) of crystalline yellow solid (**2c**), mp 135-138 °C [Lit[11] mp 139-140 °C].