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4-(*p*-Chloro)phenyl-1,2,4-triazole-3,5-dione as a novel and reusable reagent for the oxidation of 1,3,5-trisubstituted pyrazolines under mild conditions

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Abstract—4-(*p*-Chloro)phenyl-1,3,4-triazole-3,5-dione is used as an effective oxidizing agent for the oxidation of 1,3,5-trisubstituted pyrazolines to their corresponding pyrazoles under mild conditions with moderate to good yields at room temperature.
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Five-membered heterocycles such as pyrazole moieties are important constituents in many biologically active natural products and synthetic compounds of medicinal interest.[1,2] The conversion of 1,3,5-trisubstituted pyrazolines containing sensitive functional groups to their corresponding pyrazole derivatives is a difficult step to accomplish. Although a variety of reagents such as Pd/C/acetic acid,[3] cobalt soap of fatty acids,[4] lead tetraacetate,[5] mercury or lead oxide,[6] manganese dioxide,[7] potassium permanganate,[8] silver nitrate,[9] iodobenzene diacetate,[10] and zirconium nitrate[11] are all capable of effecting pyrazoline oxidation, this transformation remains capricious because these compounds are very sensitive to oxidizing agents and the reaction conditions. Moreover, most of the reported reagents produce some by-products, which either destroy the sensitive pyrazoles, or are difficult to remove.[4] Another major drawback to these procedures is the use of reagents, which are either highly toxic or produce serious disposal problems (or both).

Our goals in undertaking this work were: (a) to overcome the limitations and drawbacks of the reported methods such as tedious work-up, acidic media,[3] and safety problems [the presence of toxic transition metal cations, e.g., Co(II),[4] Pb(IV),[5] Hg(II),[6] Mn(IV and VII),[7,8] Ag(I),[9] Zr(IV)[11]]; (b) to devise a heterogeneous system, especially useful for industry, with many advantages such as reduced pollution, lower costs and simplicity in processing and handling;[12–14] (c) to develop a high-yielding synthesis of pyrazoles using a recyclable reagent.

On the other hand, among five-membered heterocyclic compounds, 4-substituted-1,2,4-triazole-3,5-diones **1** (TADs) are notable for their ability to participate in a wide range of reaction types, for example, [4+2] and [2+2] cycloadditions, ene reactions, electrophilic aromatic substitution, oxidation of alcohols to the corresponding carbonyl compounds, and aromatization of 1,4-dihydropyridines.[15,16] Therefore, we were interested to find a 'green' system for the oxidation of pyrazolines[17] and 2-imidazolines.[18] In continuation of our studies in this regard,[16] we found that 4-(*p*-chloro)phenyl-1,3,4-triazole-3,5-dione **1e** was a suitable reagent for this purpose (Fig. 1). Herein, we wish to report a simple and convenient method for the effective conversion of

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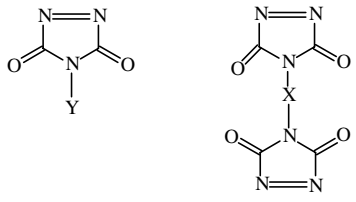


1a-f **1g-h**

Y = *n*-propyl (**1a**), *n*-butyl (**1b**), cyclohexyl (**1c**), Ph (**1d**), 4-Cl-C_6H_4- (**1e**), 3,4-$(Cl)_2$-C_6H_3- (**1f**)

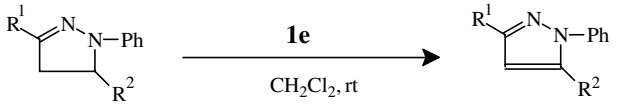
1g: X = -$(CH_2)_6$-,

1h: X = -C_6H_4-CH_2-C_6H_4-

Figure 1.

1,3,5-trisubstituted pyrazolines **2** to their corresponding pyrazoles **3** using 4-(*p*-chloro)phenyl-1,3,4-triazole-3,5-dione **1e** under mild conditions (Scheme 1 and Table 1).

A good range of 1,3,5-trisubstituted pyrazolines were subjected to aromatization in the presence of 4-(*p*-chloro)phenyl-1,3,4-triazole-3,5-dione **1e** in CH_2Cl_2 (Scheme 1).[19,20] The oxidation reactions were performed under mild conditions at room temperature with moderate to good yields. The crude 1,3,5-trisubstituted pyrazoles **3** were obtained by simple filtration and evaporation of the solvent. Highly pure pyrazoles **3** could be obtained simply by column chromatography (eluent EtOAc–*n*-hexane, 2:8). The results and reaction conditions are given in Table 1. Monitoring of the reaction is very simple as 4-(*p*-chloro)phenyl-1,3,4-triazole-3,5-dione **1e** has a deep red color and is soluble in CH_2Cl_2 and is converted to 4-(*p*-chloro)phenyl urazole **4**, which is white in color and is insoluble in CH_2Cl_2. This also simplifies the work-up as 4-(*p*-chloro)phenyl urazole **4** was isolated by simple filtration. The results and reaction conditions are given in Table 1. 4-(*p*-Chloro)phenyl urazole **4** can be readily converted to 4-(*p*-chloro)phenyl-1,3,4-triazole-3,5-dione[21] **1e** and reused (Scheme 2).



2 **3**

Scheme 1.

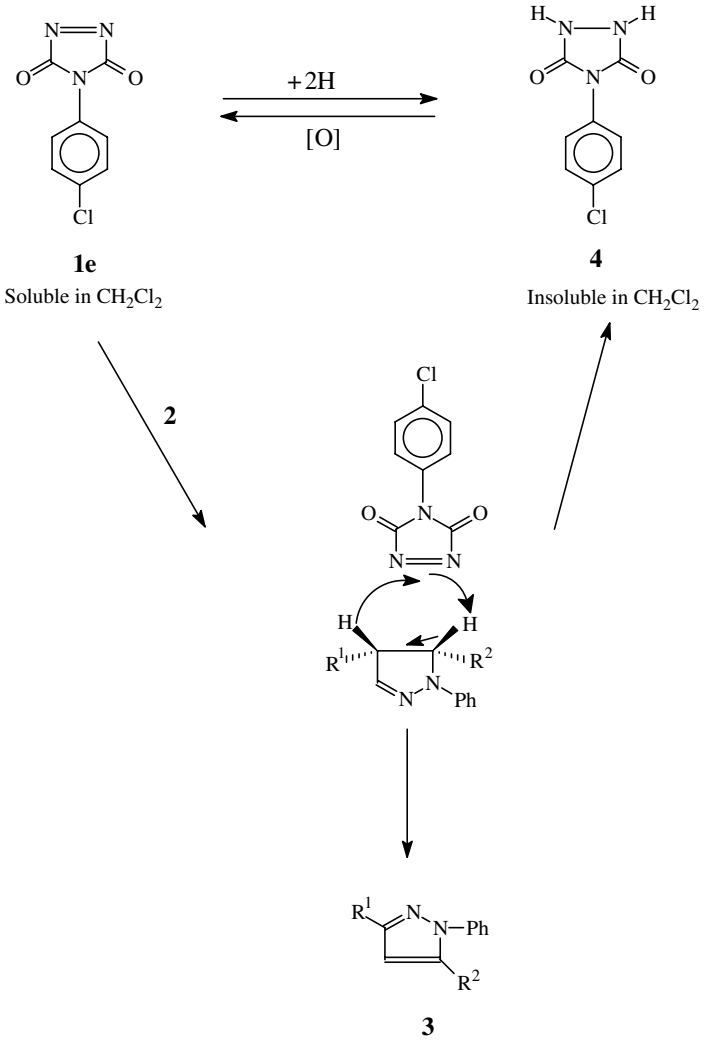
In continuation of our studies on the oxidation of 2-imidazolines[18] we were also interested in using 4-substituted-1,3,4-triazole-3,5-diones **1** for the oxidation of different kinds of imidazoline derivatives **5** but the reactions were sluggish and not practical. Several efforts for optimizing the reaction conditions failed and the yields of the desired products (i.e., imidazoles **6**) were very low and some unidentified by-products were also produced (Scheme 3).

In conclusion, a practical and efficient oxidation of 1,3,5-trisubstituted pyrazolines has been achieved by the methodology described. The reagent can be used for the aromatization of a wide variety of pyrazolines derivatives under safe conditions.

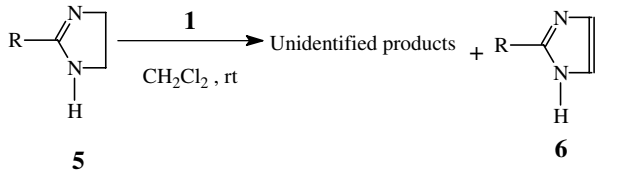
Table 1. Oxidation of 1,3,5-trisubstituted pyrazolines **2a**–**n** to their corresponding pyrazoles **3a**–**n** with 4-(*p*-chloro)phenyl-1,3,4-triazole-3,5-dione **1e** in CH_2Cl_2 at room temperature

Substrate	Product[a]	R^1	R^2	Reag./Subst.[b]	Time (min)	Yield (%)[c]	Melting point (°C)	
							Found	Literature
2a	**3a**	2-Naphthyl	*o*-$CH_3C_6H_4$	1.25	25	70	148–150	151–152[17c]
2b	**3b**	Ph	Ph	1.00	15	70	133–134	138–139[10]
2c	**3c**	*p*-$CH_3C_6H_4$	*m*-$CH_3C_6H_4$	1.50	30	65	94–96	95–98[17c]
2d	**3d**	*p*-$CH_3OC_6H_4$	*o*-$CH_3C_6H_4$	1.25	30	60	70–71	70–72[17c]
2e	**3e**	*p*-$CH_3OC_6H_4$	*m*-$CH_3C_6H_4$	1.25	35	68	80–82	84–86[17c]
2f	**3f**	*p*-$CH_3OC_6H_4$	Ph	1.50	25	76	74–76	75–77[17c]
2g	**3g**	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	1.50	35	62	98–100	101–103[17c]
2h	**3h**	2-Naphthyl	*m*-$CH_3C_6H_4$	1.50	35	65	90–91	75–78[17c]
2i	**3i**	2-Naphthyl	*p*-ClC_6H_4	1.25	45	60	129–130	130–133[17c]
2j	**3j**	*p*-$CH_3C_6H_4$	2-Furyl	1.50	35	63	96–98	93–95[10]
2k	**3k**	*p*-$CH_3OC_6H_4$	*o*-ClC_6H_4	1.50	30	70	66–68	63–65[17c]
2l	**3l**	Ph	*p*-$NO_2C_6H_4$	1.50	35	66	144–146	142–143[11]
2m	**3m**	Ph	*p*-$CH_3OC_6H_4$	1.50	30	65	79–80	77–78[10]
2n	**3n**	Ph	*m*ClC_6H_4	1.50	35	73	112–114	114–115[11]

[a] All of the isolated products were known compounds and their spectra and physical data have been reported in the literature.[17]
[b] Molar ratio of **1e**.
[c] Isolated pure yields after column chromatography (eluent EtOAc–*n*-hexane, 2:8).



Scheme 2.



Scheme 3.

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References and notes

1. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, 1015.
2. (a) Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd ed.; John Wiley & Sons: New York, 1992; p 294; (b) Gao, X. C.; Cao, H.; Zhang, L. Q.; Zhang, B. W.; Cao, Y.; Huang, C. H. *J. Mater. Chem.* **1999**, *9*, 1077–1080; (c) Claramunt, R. M.; Lopez, C.; Garcia, M. D. L. A.; Pierrot, M.; Giorgi, M.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2049–2053; (d) Froggett, J. A.; Hockley, M. H.; Titman, R. B. *J. Chem. Res. (S)* **1997**, 30–31; (e) Baldwin, J. E.; Pritchard, G. J.; Rathmell, R. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2906–2908; (f) Voznesenskii, S. A.; Belen'kii, L. I.; Dudinov, A. A.; Struchkova, M. I.; Krayushkin, M. M. *Mendeleev Commun.* **1998**, 1–42; (g) Donohue, A. C.; Pallich, S.; McCarthy, T. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1817–2822; (h) Elgemeie, G. H.; Matwally, N. H. *J. Chem. Res. (S)* **1999**, 384–385; (i) Chang, K. T.; Choi, Y. H.; Kim, S. H.; Yoon, Y. J.; Lee, W. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 207–210.
3. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955–3957.
4. Shah, J. N.; Shah, C. K. *J. Org. Chem.* **1978**, *43*, 1266–1267.
5. Goldstone, W. A. F.; Norman, R. O. C. *J. Chem. Soc., Chem. Commun.* **1966**, 1536–1540.
6. Auwers, K.; Heimke, P. *Liebigs Ann.* **1927**, *458*, 186–220.
7. Bhatnagar, I. G.; George, M. V. *Tetrahedron* **1968**, *24*, 1293–1298.

8. Smith, L. I.; Howard, K. L. *J. Am. Chem. Soc.* **1943**, *65*, 159–164.
9. Dodwadmath, R. P.; Wheeler, T. S. *Proc. Ind. Acad. Sci.* **1935**, *2A*, 438–451.
10. Singh, S. P.; Kumar, D.; Prakash, O.; Kapoor, R. P. *Synth. Commun.* **1997**, *27*, 2683–2689.
11. Sabitha, G.; Kumar Reddy, G. S. K.; Reddy, Ch. S.; Fatima, N.; Yadav, J. S. *Synthesis* **2003**, 1267–1271.
12. Varma, R. S. *Green Chem.* **1999**, *1*, 43–55.
13. Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074.
14. Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91.
15. (a) Mallakpour, S. E.; Zolfigol, M. A. *Indian J. Chem.* **1995**, *34B*, 183, and references cited therein; (b) Mallakpour, S. E.; Zolfigol, M. A. *Indian J. Chem.* **1995**, *34B*, 302; (c) Mallakpour, S. E.; Zolfigol, M. A. *Indian J. Chem.* **1998**, *37B*, 1001; (d) Mallakpour, S. E.; Zolfigol, M. A. *Indian J. Chem.* **1999**, *38B*, 777; (e) Zolfigol, M. A.; Chehardoli, G.; Mallakpour, S. E. *Synth. Commun.* **2003**, *33*, 833; (f) Zolfigol, M. A.; Nasr-Isfahani, H.; Mallakpour, S. E.; Safaiee, M. *Synlett* **2005**, 761, and our references cited therein.
16. Zolfigol, M. A.; Ghorbani Choghamarani, A.; Shahamirian, M.; Safaiee, M.; Mohammadpoor-Baltork, I.; Mallakpour, S.; Abdollahi-Alibeik, M. *Tetrahedron Lett.* **2005**, *46*, 5581.
17. (a) Zolfigol, M. A.; Azarifar, D.; Maleki, B. *Tetrahedron Lett.* **2004**, *45*, 2181; (b) Azarifar, D.; Zolfigol, M. A.; Maleki, B. *Bull. Korean Chem. Soc.* **2004**, *25*, 23; (c) Azarifar, D.; Zolfigol, M. A.; Maleki, B. *Synthesis* **2004**, 1744.
18. (a) Mohammadpoor-Baltork, I.; Zolfigol, M. A.; Abdollahi-Alibeik, M. *Synlett* **2004**, 2803; (b) Mohammadpoor-Baltork, I.; Zolfigol, M. A.; Abdollahi-Alibeik, M. *Tetrahedron Lett.* **2004**, *45*, 8687; (c) Abdollahi-Alibeik, M.; Mohammadpoor-Baltork, I.; Zolfigol, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6079.
19. Chemicals were purchased from Fluka, Merck, Riedeldehaen 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 authentic samples. All 1,3,5-trisubstituted pyrazolines,[22] 4-substituted triazolinediones,[15,21] 2-imidazolines[18] were synthesized according to our previously reported procedure.
20. Typical procedure for oxidation of pyrazolines: a mixture of 1,3,5-triphenylpyrazoline **2b** (0.301 g, 1 mmol) and 4-(*p*-chloro)phenyl-1,3,4-triazole-3,5-dione **1e** (0.209 g, 1 mmol) in CH_2Cl_2 (20 mL) was stirred vigorously at room temperature for 15 min. The crude 1,3,5-trisubstituted pyrazole **3** was obtained by simple filtration and evaporation of the solvent. Highly pure pyrazole **3** could be obtained simply by column chromatography (eluent EtOAc–*n*-hexane, 2:8). The solvent was evaporated and the pyrazole **3b** was obtained as a yellow solid in 70% yield, mp 133–134 °C [Lit.[10] mp 138–139 °C]; IR (KBr): 3120, 3060, 1595, 1482 (cm^{-1}); ^{1}H NMR ($CDCl_3$, 90 MHz): δ 6.86 (1H, S, CH), 7.32 (10H, m, Ar), 7.96 (5H, m, Ar).
21. (a) Zolfigol, M. A.; Zebarjadian, M. H.; Chehardoli, G.; Mallakpour, S. E.; Shamsipur, M. *Tetrahedron* **2001**, *57*, 1627; (b) Zolfigol, M. A.; Chehardoli, G. A.; Mallakpour, S. E. *Synth. Commun.* **2003**, *33*, 833; (c) Zolfigol, M. A.; Mallakpour, S. E.; Madrakian, E.; Ghaemi, E. *Indian J. Chem.* **2000**, *39B*, 308; (d) Zolfigol, M. A.; Chehardoli, G. A.; Mallakpour, S. E.; Nasr-Isfahani, H. *Synth. Commun.* **2001**, *31*, 1965; (e) Zolfigol, M. A.; Torabi, M.; Mallakpour, S. E. *Tetrahedron* **2001**, *57*, 8381, and our other references cited therein; (f) Zolfigol, M. A.; Bagherzadeh, M.; Chehardoli, G. A.; Mallakpour, S. E.; Mamaghani, M. *J. Chem. Res. (S)* **2001**, 390; (g) Zolfigol, M. A.; Salehi, P.; Mallakpour, S. E.; Torabi, M. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1673.
22. Azarifar, D.; Shaebanzadeh, M. *Molecules* **2002**, *7*, 885.