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4-Phenyl-1,2,4-triazole-3,5-dione as a novel and reusable reagent for the aromatization of 1,4-dihydropyridines under mild conditions

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Abstract—4-Substituted 1,3,4-triazole-3,5-diones were used as effective and recyclable oxidizing agents for the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives under mild conditions with good to excellent yields.

Five- and six-membered heterocyclic compounds are important components of biologically active natural products and synthetic compounds of medicinal interest.[1] Among them, 4-substituted Hantzsch dihydropyridines are analogues of NADH coenzymes and are an important class of drugs.[2] Dihydropyridines are often produced in a syntheses and have to be oxidized to pyridines.[3] Numerous reagents and procedures have been recommended for this purpose, such as ferric or cupric nitrates on a solid support (clayfen or claycop), ceric ammonium nitrate, clay-supported cupric nitrate accompanied by ultrasound-promotion,[3] manganese dioxide or DDQ, nitric oxide, bismuth nitrate pentahydrate, PCC, tetrakis-pyridine cobalt(II) dichromate (TPCD), nicotinium dichromate,[4] the N_2O_4 complex of 18-crown-6,[5] *S*-nitrosoglutathione, diphenylpicrylhydrazyl, and benzoyl peroxide as free radical oxidizing agents, $KMnO_4$, CrO_3, HNO_3, HNO_2, *tert*-butylhydroperoxide, silica gel supported ferric nitrate (silfen), N_2O_3, photochemical oxidation, MCl_x/$NaNO_2$/wet SiO_2,[6] silica chloride/$NaNO_2$/wet SiO_2,[7] H_2O_2/$Co(OAc)_2$,[8] $NaHSO_4$/$Na_2Cr_2O_7$/wet SiO_2,[9] peroxydisulfate-cobalt(II),[10] $Zr(NO_3)_4$,[11] hypervalent iodine reagents,[12] Co(II) catalyzed auto oxidation,[13] inorganic acidic salts, and sodium nitrite or nitrate,[14–18] I_2–MeOH,[19] selenium dioxide,[20] and heteropolyacid/$NaNO_2$/wet SiO_2.[21] A literature survey showed that three other systems that have been used for dehydrogenation of 1,4-dihydropyridines are catalysis by cytochrome-P-450,[22] electrochemical,[23] and a homogenous complex of palladium as a catalyst.[24]

Although a variety of reagents are capable of effecting these oxidations,[1–21] this transformation is not always so easy and can be a difficult step if the substrates have functional groups within the molecule sensitive to the oxidizing agent and reaction conditions. Most of the reported reagents produce by-products, which are difficult to remove. Another major drawback in several cases is the use of reagents, which are either highly toxic or present serious disposal problems (or both). Therefore, we decided to develop new reagents to overcome these limitations. In addition, both a clean and easy work-up were important.

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,

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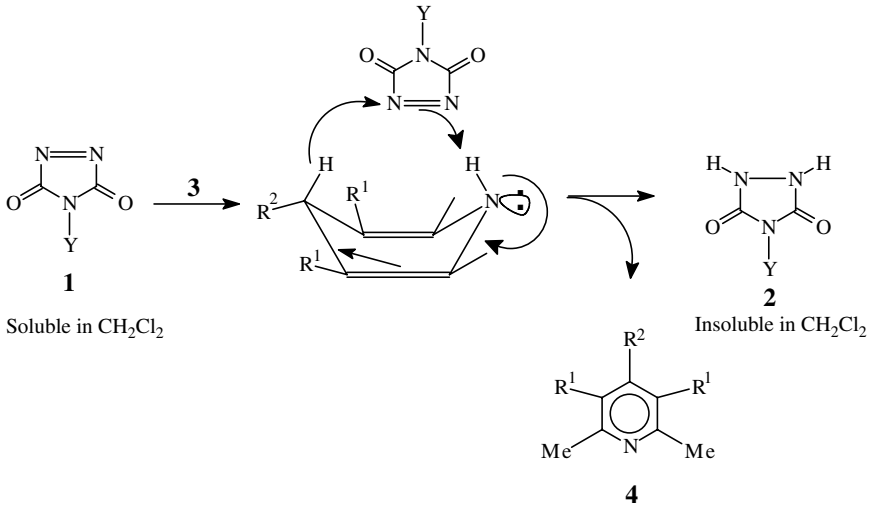
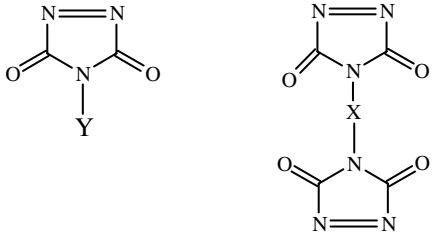


Scheme 1.

ene reactions, electrophilic aromatic substitution, and oxidation of alcohols to aldehydes and ketones.[25–27] In continuation of our studies on the chemistry of 4-substituted 1,2,3-triazole-3,5-diones,[28] we were interested in using compounds of type **1** for the aromatization of 1,4-dihydropyridines via the mechanism outlined in Scheme 1. Herein, we report a simple method for the effective oxidation of 1,4-dihydropyridines **3** to the corresponding pyridines **4** under mild conditions (Schemes 2 and 3).



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

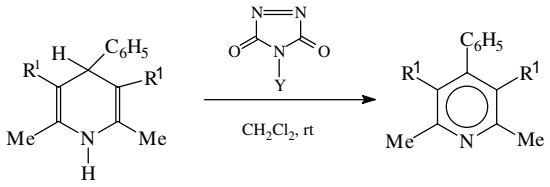
Y= *n*-propyl, *n*-butyl, cyclohexyl, Ph, 4-Cl-C_6H_4-, 3,4-$(Cl)_2$-C_6H_3-

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

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

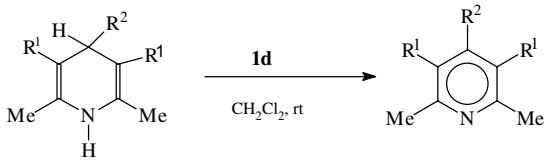
At first, different 4-substituted 1,3,4-triazole-3,5-diones **1a**–**h** were treated with methyl-4-phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate **3d** (Scheme 2). The results are given in Table 1. As shown, 4-phenyl-1,2,4-triazole-3,5-dione **1d** was a good candidate for this purpose due to its high reactivity and easy preparation.[26]

A good range of 1,4-dihydropyridines **3** were subjected to the oxidation reaction in the presence of 4-phenyl-1,3,4-triazole-3,5-dione **1d** in dichloromethane at room temperature (Scheme 3). The oxidation reactions were performed under mild conditions and gave excellent yields (Table 2).[29]



3d **4d**

Scheme 2.



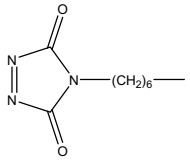
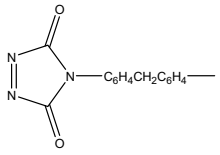
3 **4**

Scheme 3.

This oxidation reaction was carried out by mixing the 4-substituted 1,3,4-triazole-3,5-dione **1d**, and 1,4-dihydropyridine **3** in CH_2Cl_2 as the solvent. Monitoring of the reaction was very simple, the 4-substituted 1,3,4-triazole-3,5-dione is a deep red color and is soluble in CH_2Cl_2 and is converted into the 4-substituted urazole **2**, which is white and is insoluble in CH_2Cl_2. The reaction is rapid and the work-up was straightforward requiring simple filtration of the urazole. Highly pure pyridine derivatives **4** could be obtained by passing the filtrate through a short pad of silica gel followed by evaporation of the solvent. The results and reaction conditions are given in Tables 1 and 2. Urazole **2** can be readily converted back to the 4-substituted 1,3,4-triazole-3,5-dione[26–28] and reused.

In continuation of our studies on the chemistry of 2-imidazolines[30–32] and pyrazolines[33–35] we were also

Table 1. Aromatization of 1,4-dihydropyridine **3d** to the corresponding pyridine **4d** using 4-substituted 1,3,4-triazole-3,5-diones **1a**–**f** and bis-1,3,4-triazole-3,5-diones **1g**–**h** in dichloromethane at room temperature

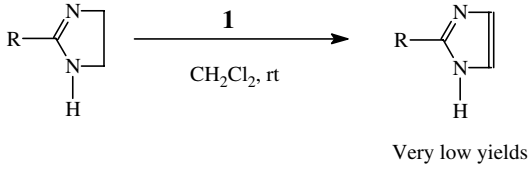
Entry	Reagent **1**	Y	Reagent/substrate (mmol) **1**	Time (min)	Yield[a] (%)
1	**1a**	*n*-Propyl	1.55	90	92
2	**1b**	*n*-Butyl	1.65	90	93
3	**1c**	Cyclohexyl	1.7	120	91
4	**1d**	C_6H_5	1.1	25	88
5	**1e**	4-Cl–C_6H_4–	1.2	35	92
6	**1f**	3,4-$(Cl)_2$–C_6H_3–	2	120	85
7	**1g**		1.3	55	94
8	**1h**		0.78	45	92

[a] Isolated yield.

Table 2. Aromatization of 1,4-dihydropyridines **3** to the corresponding pyridine derivatives **4** using 4-phenyl-1,2,4-triazol-3,5-dione **1d** in dichloromethane at room temperature

Entry	Substrate	Product	R^1	R^2	Reagent/substrate (mmol)	Time (min)	Yield (%)[a]
1	**3a**	**4a**	COOMe	Me	1.1	15	87
2	**3b**	**4b**	COOMe	Et	1.055	15	99
3	**3c**	**4c**	COOMe	*n*-Propyl	1.055	15	92
4	**3d**	**4d**	COOMe	C_6H_5	1.1	25	88
5	**3e**	**4e**	COOMe	2-Thienyl	1.25	20	80
6	**3f**	**4f**	COOMe	4-NO_2–C_6H_4–	1.2	20	92
7	**3g**	**4g**	COOMe	3-NO_2–C_6H_4–	1.35	25	95
8	**3h**	**4h**	COOMe	4-Br–C_6H_4–	1.1	15	98
9	**3i**	**4i**	COOMe	2-Br–C_6H_4–	1.25	10	96
10	**3j**	**4j**	COOMe	3-py	1.25	25	92
11	**3k**	**4k**	COOMe	2-CH_3O–C_6H_4–	1.25	10	87
12	**3l**	**4l**	COOMe	3-NO_2–C_6H_4–	1.2	20	91
13	**3m**	**4m**	COOEt	H	1	3	91
14	**3n**	**4n**	COOEt	Me	1.1	10	91
15	**3o**	**4o**	COOEt	Et	1.05	10	99
16	**3p**	**4p**	COOEt	Ph	1.1	5	93
17	**3q**	**4q**	COOEt	3-NO_2–C_6H_4–	1.1	10	95
18	**3r**	**4r**	COOEt	4-NO_2–C_6H_4–	1.1	8	98
19	**3s**	**4s**	COOEt	2-Br–C_6H_4–	1.1	5	93
20	**3t**	**4t**	COOEt	4-Br–C_6H_4–	1.1	7	98
21	**3u**	**4u**	COOEt	2-CH_3O–C_6H_4–	1	3	94
22	**3v**	**4v**	COOEt	2-Thienyl	1.15	10	84
23	**3w**	**4w**	COOEt	2-py	1.2	10	87
24	**3x**	**4x**	COOEt	4-py	1.2	20	91

[a] Isolated yields.



Scheme 4.

interested in using 4-substituted 1,3,4-triazole-3,5-diones **1** for the oxidation of imidazolines but the reactions were sluggish and not practical (Scheme 4).

In conclusion, the recycling and reusing of the reagents, the easy and clean work-up, and the high yields make this an attractive methodology.

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