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Metal-Free Oxidation of Urazole and 1,4-Dihydropyridine Derivatives Under Mild and Heterogeneous Conditions by Nitro Urea, Derived from Urea Nitrate, and Silica Sulfuric Acid

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Abstract: Mild combination of nitro urea, derived from urea nitrate, and silica sulfuric acid (SiO_2OSO_3H) might act as an efficient oxidizing media, which could be able to oxidize different types of heterocyclic compounds including urazoles and 1,4-dihydropyridines. The process presented here is operationally simple, environmentally benign, and reactions have been mildly carried out in dichloromethane at room temperature.

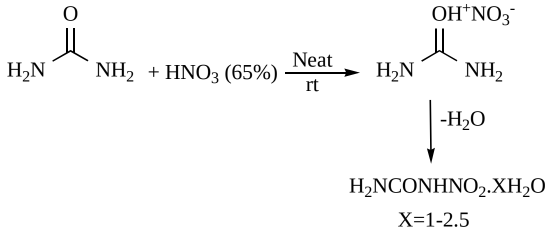
Keywords: Urazole, 1,4-dihydropyridine, urea nitrate, nitro urea, silica sulfuric acid.

INTRODUCTION

Five- and six-membered heterocyclic compounds often play important roles in biologically active natural products and synthetic compounds of medicines [1]. Among them, urazoles and 1,4-dihydropyridines have attracted considerable attention. The oxidation of Hantzsch 1,4-dihydropyridines (DHPs), a class of model compounds of NADH coenzyme [2], has attracted continuing interest of organic chemists over the years [3]. The oxidation of these compounds to corresponding pyridines has been extensively studied in view of the pertinence of the reaction to the metabolism of Hantzsch esters and the calcium channel blocking drugs used in the treatment of various cardiovascular disorders [4]. In recent years, it was found that drugs such as nifedipine and niguldipine undergo redox processes due to the catalysis of cytochrome P-450 in the liver during their metabolism [5]. Also 1,2,4-Triazole-3,5-diones are important class of five-membered heterocyclic compounds, which can be prepared from the oxidation of urazole derivatives. They have been used as substrate and reagent both in various organic transformations [6-10]. Oxidation of urazoles by different oxidants is a common way for the preparation of triazolinediones. However, in some of these procedures by-products are produced or the products decompose under the reaction conditions, and/or the workup is difficult [11]. In recent years, several reports on the oxidation of urazoles and 1,4-dihydropyridines have been reported [12-18]. Most of these reported procedures require use of strong and toxic oxidants, harsh conditions, long reaction times, necessity of excess reagent, formation of by-products, laborious work-up, and poor yields of the target products.

RESULTS AND DISCUSSION

Recently, we have reported various procedures for the generation of nitronium ion (NO_2^+), which were applied in different organic transformations [19-25]. In continuation of our investigations, we decided to explore an efficient, mild, heterogeneous and metal-free oxidizing system for the oxidation of urazoles and dihydropyridines. In this light, we interested to synthesize nitro urea *via* reaction of urea with nitric acid to produce urea nitrate, which immediate dehydrated to nitro urea (Scheme **1**) [26,27].



Scheme 1.

Fig. (**1**) shows the mass spectrum of nitro urea, which molecular ion peak appears at m/e= 105. Also two major peaks appears at m/e= 46 (NO_2^+) and m/e= 60 (urea cation).

After considering on the properties of nitro urea ($NH_2CONHNO_2.xH_2O$), we found that this reagent has oxidizing property in the presence of an acid. Nitro urea ($NH_2CONHNO_2.xH_2O$) can realize nitronium ion (NO_2^+) in the presence of silica sulfuric acid (SiO_2-OSO_3H), which is able to oxidize different types of organic compounds.

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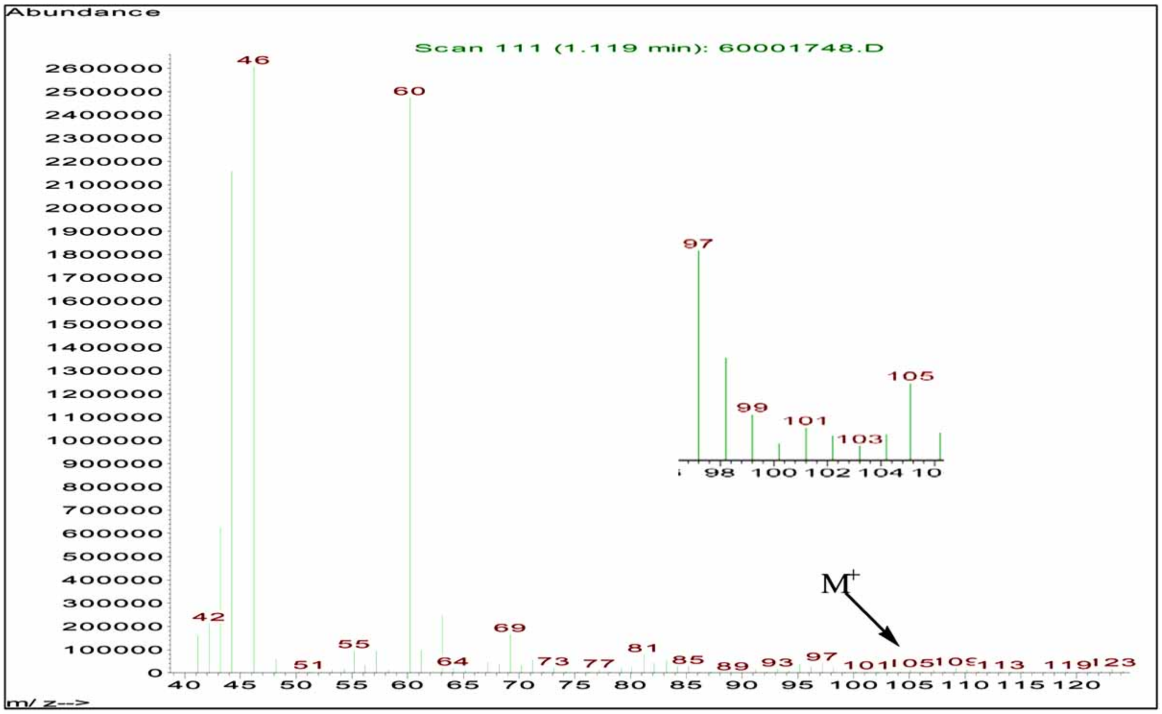
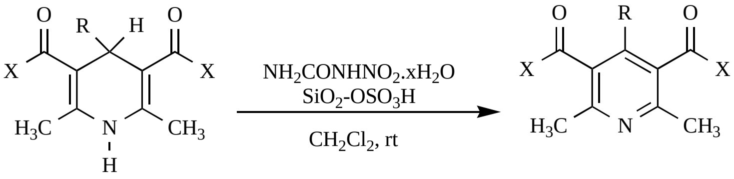
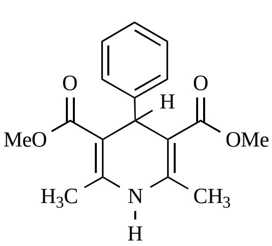


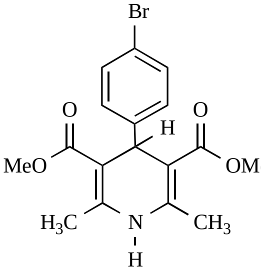
Fig. (1). Mass spectrum of nitro urea ($NH_2CONHNO_2.xH_2O$).

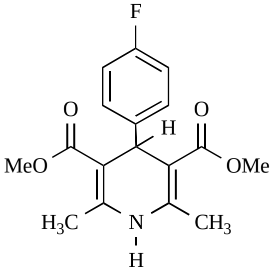


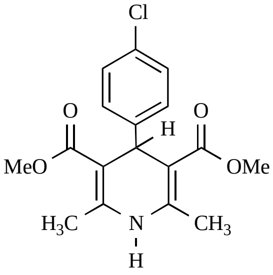
1 **2**

X= $-OCH_3$ or $-OCH_2CH_3$

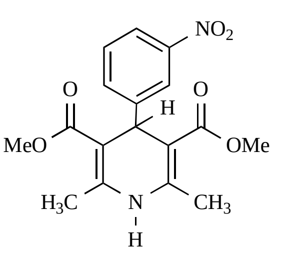


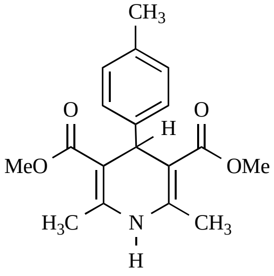


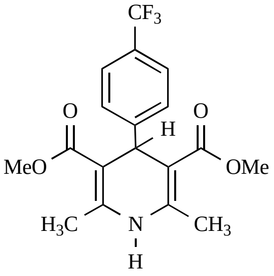


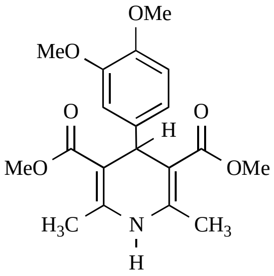


a **b** **c** **d**



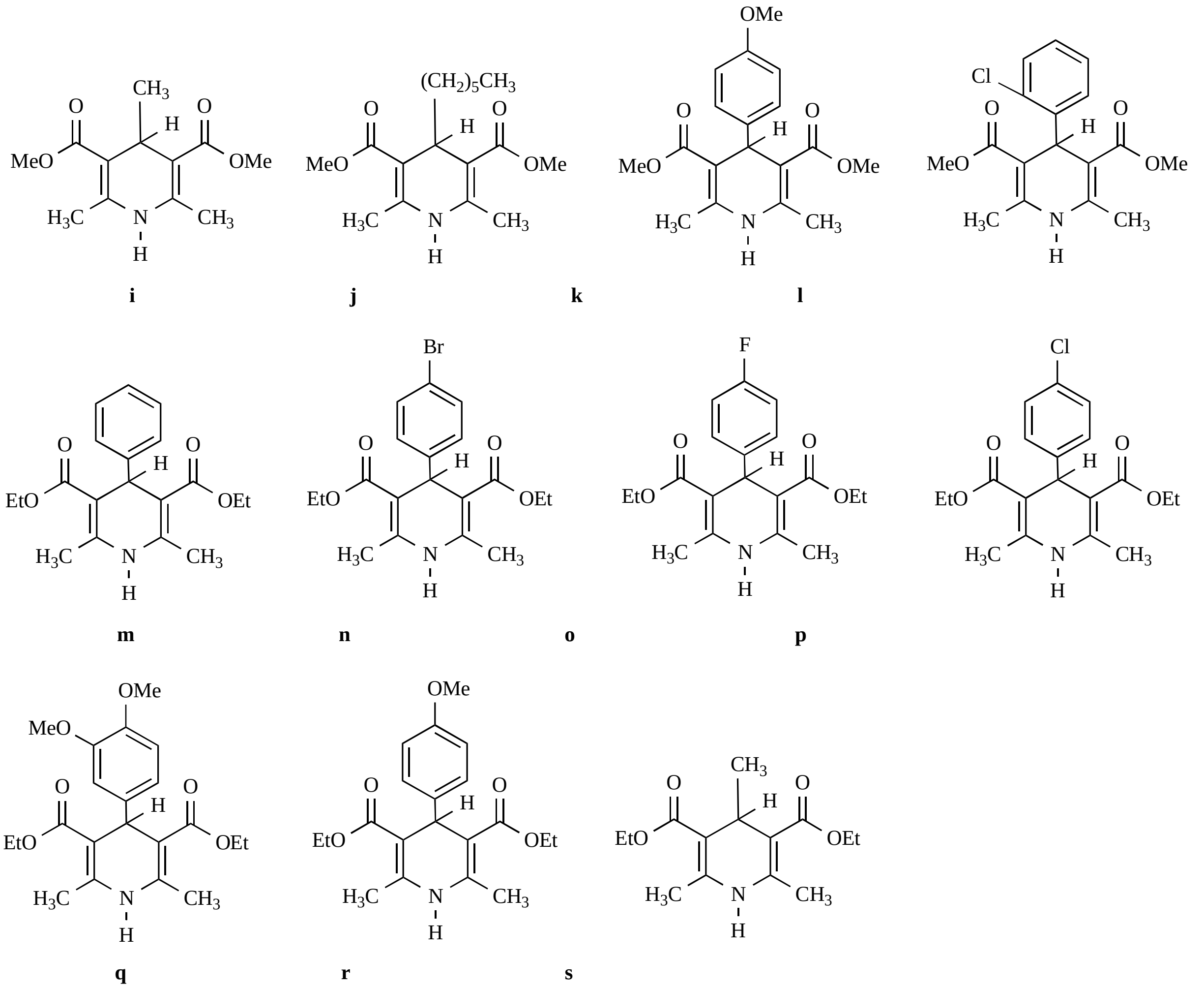






e **f** **g** **h**

(Scheme 2). Contd…..



Scheme 2.

Table 1. Oxidation of 1,4-Dihydropyridines 1 to the Corresponding Pyridines 2 Using Nitro Urea I and Silica Sulfuric Acid II in Dichloromethane at Room Temperature

Entry	Substrate	Product	Substrate/Reagents[a]		Time (Min)	Yield (%)[b]
			I	II		
1	**1a**	**2a**	0.56	0.7	45	96
2	**1b**	**2b**	0.56	0.7	35	91
3	**1c**	**2c**	0.64	0.8	20	98
4	**1d**	**2d**	0.56	0.7	55	99
5	**1e**	**2e**	0.56	0.7	30	95
6	**1f**	**2f**	0.56	0.7	30	92
7	**1g**	**2g**	1.46	1.82	10	94
8	**1h**	**2h**	0.56	0.7	180	98
9	**1i**	**2i**	0.56	0.7	6 h	97
10	**1j**	**2j**	0.56	0.7	130	90
11	**1k**	**2k**	0.56	0.7	200	99
12	**1l**	**2l**	0.56	0.7	130	84
13	**1m**	**2m**	0.56	0.7	240	99

(Table 1). Contd…..

Entry	Substrate	Product	Substrate/Reagents[a]		Time (Min)	Yield (%)[b]
			I	II		
14	**1n**	**2n**	0.96	1.2	15	94
15	**1o**	**2o**	0.96	1.2	180	99
16	**1p**	**2p**	0.96	1.2	240	99
17	**1q**	**2q**	0.56	0.7	120	99
18	**1r**	**2r**	0.56	0.7	180	99
19	**1s**	**2s**	0.56	0.7	220	93

[a] **I** and **II** refer to grams of nitro urea and silica sulfuric acid, respectively. [b] Isolated yield.

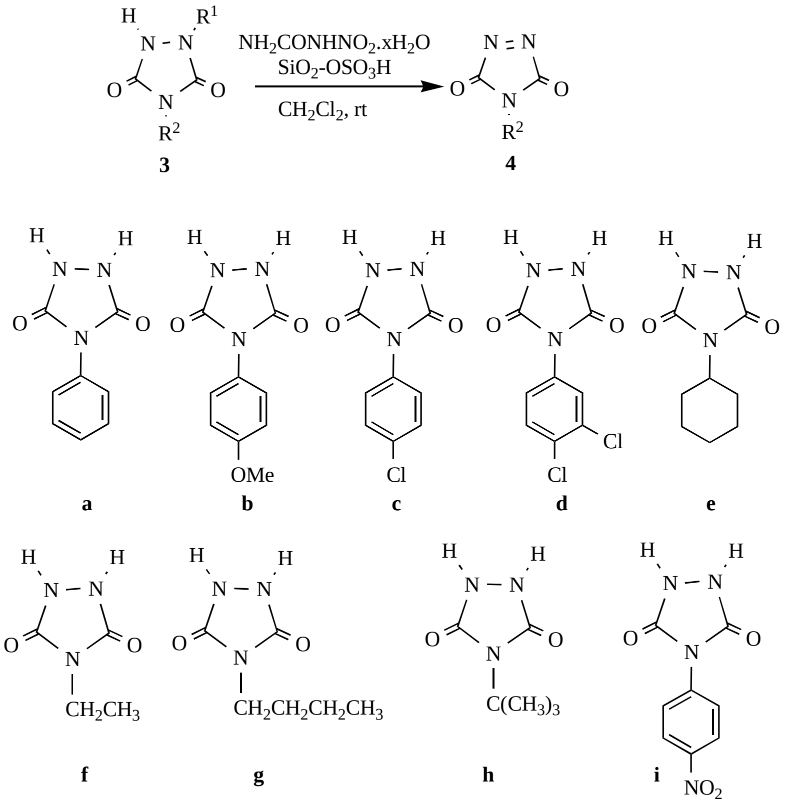
Consequently herein we disclosed a new oxidative protocol for the conversion of Hantzsch 1,4-dihydropyridines **1** to the corresponding pyridines **2** using nitro urea ($NH_2CONHNO_2.xH_2O$) **I**, and silica sulfuric acid (SiO_2-OSO_3H) **II** in dichloromethane, as solvents, at room temperature (Scheme **2** and Table **1**).

Oxidation of 1,4-dihydropyridines was carried out heterogeneously under mild conditions. Oxidation reaction was easily performed by mixing 1 mmol of dihydropyridine, and appropriate amounts of nitro urea and silica sulfuric acid, then stirr the resulting mixture at room temperature. After reaction completion, pure product can easily be obtained by simple filtration and evaporation of the solvent.

Also different types of 4-substituted urazoles **3** were converted to the 4-substituted-1,2,4-triazole-3,5-diones **4** by the same reagents and conditions (Scheme **3** and Table **2**).

Oxidation of urazoles has been heterogeneously performed under mild conditions. All reaction components except pink-to-red color triazolinedione are insoluble in the reaction solvent. Therefore, 4-substituted-1,2,4-triazole-3,5-diones were obtained easily by mixing of urazole, nitro urea and a catalytic amount of silica sulfuric acid; then stirring of this mixture at room temperature. Pure products can be easily isolated from the reaction media by washing the reaction mixture with dichloromethane, simple filtration and evaporation of the solvent. The results of Table **2** show that the oxidation of urazoles by nitro urea needs only a catalytic amount of acid. Also reasonable turn over frequency (TOF) of catalyst was observed.

In conclusion, in this research project, an effective and new oxidizing media has been introduced for the oxidation of urazoles and Hantzsch 1,4-dihydropyridines under heterogeneous conditions. Furthermore, this method exhibits



Scheme 3.

Table 2. Oxidation of Urazoles to the Corresponding Triazolinediones Using Nitro Urea I and Catalytic Amounts of Silica Sulfuric Acid II in Dichloromethane at Room Temperature[a]

Entry	Substrate	Product	Time (Min)	Yield (%)[b]	TOF (min^{-1})
1	**3a**	**4a**	60	95	12.0
2	**3b**	**4b**	105	99	7.1
3	**3c**	**4c**	105	97	7.0
4	**3d**	**4d**	150	91	4.6
5	**3e**	**4e**	180	95	4.0
6	**3f**	**4f**	90	98	8.2
7	**3g**	**4g**	105	99	7.1
8	**3h**	**4h**	150	99	5.0
9	**3i**	**4i**	10.5 h	90	1.1

[a] Molar ratio of reaction components: urazole/nitro urea/silica sulfuric acid for entries 1-8: (1 mmol/0.32 g /0.05 g); for entry 9: (1 mmol/0.48 g /0.05 g). [b] Isolated yields.

substrate versatility, non-toxic conditions and mild reaction conditions, and easy and clean work-up of products.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The oxidation products were characterized by comparison of their spectral (IR, ^1H NMR, and ^{13}C NMR) and physical data with authentic samples.

Preparation of Nitro Urea ($NH_2CONHNO_2.xH_2O$)

In a 50-mL round-bottomed flask, 4 mL of HNO_3 (65%) and 3.46 g of urea was stirred for 2 hours, and a white crystalline solid ($NH_2CONHNO_2.xH_2O$) was obtained quantitatively. M.p. 156-158.4 °C (Ref. [27] 157-159°C); MS (70 eV): *m*/*z* = 105 (M+), 91, 69, 63, 60, 46 (base peak, NO_2^+), 44.

Aromatization of Dimethyl 4-(4-trifluoromethylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate with Nitro Urea and Silica Sulfuric Acid

To a solution of compound **1g** (0.369 g, 1.0 mmol) in CH_2Cl_2 (10 mL), $NH_2CONHNO_2.xH_2O$ (1.46 g) and SiO_2-OSO_3H (1.82 g) were added. Reaction mixture was stirred at room temperature for 10 min (the reaction progress was monitored by TLC) and then filtered. Anhydrous Na_2SO_4 (3 g) was added to the filtrate and filtered off after 20 min. The residue was washed with CH_2Cl_2 (4×5 mL). Finally solvent was removed and product **2g** was obtained in 94 % yield (0.345 g). Pale yellow solid; mp 75-76 ºC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (d, 2H, J= 8 Hz), 7.39-7.37 (d, 2H, J= 8 Hz), 3.55 (s, 6H), 2.62 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 156.0, 144.8, 140.2, 131.2-130.2 (q, $^1J_{C-F}$, 128 Hz), 128.4, 126.4, 125.2-125.0 (q, $^1J_{C-F}$, 12 Hz), 122.5, 25.3, 23.03 ppm; MS (70 eV): *m*/*z* = 369 (M+), 354, 338, 310, 294, 278, 264, 250, 224 (base peak), 209, 192, 164,149, 132,106, 91, 77, 59, 42.

Oxidation of 4-phenylurazole 3a to 4-phenyl-1,2,4-triazoline-3,5-dione 4a with Nitro Urea and Catalytic Amounts of Silica Sulfuric Acid

A suspension of 4-phenylurazole **3a** (0.177 g, 1 mmol), $NH_2CONHNO_2.xH_2O$ (0.32 g) and SiO_2-OSO_3H (0.05 g) in dichloromethane (10 mL) was stirred at room temperature for 60 min and then filtered. Anhydrous Na_2SO_4 (3 g) was added to the filtrate and filtered off after 20 min. The residue was washed with CH_2Cl_2 (20 mL). Finally CH_2Cl_2 was removed and 4-phenyl-1,2,4-triazoline-3,5-dione **4a** was obtained in 95% yield (0.166 g) as red crystalline solid. Mp 172-174 ºC (Lit. [28] mp 168-175 ºC); ^1H NMR (90 MHz, $CDCl_3$): δ = 7.49 (s) ppm; ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 158.0 (C=O), 129.9, 129.8, 129.0, 124.3 ppm.

Caution

Urea nitrate and nitro urea are both potential explosives and must be handled with care, similarly to ammonium nitrate (The Health and Safety at Work Act 1974, Chapter 37, HMSO ISBN 0 10 543774 3).

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