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$MnSO_4.H_2O$: A highly efficient and inexpensive catalyst for the synthesis of benzo-2-pyrones and benzopyrazines

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Efficient and direct protocols for the preparation of some heterocyclic compounds such as benzo-2-pyrones and benzopyrazines in the presence of manganese (II) sulfate monohydrate ($MnSO_4 \cdot H_2O$) as an inexpensive catalyst have been described. These novel methods are very cheap and they include some advantages, such as excellent yields, use of the safe catalyst and readily available starting materials, and simple work-up procedure.

Keywords: $MnSO_4 \cdot H_2O$; Benzo-2-pyrones, Benzopyrazine; Catalyst.

INTRODUCTION

Development of methods including preparation of heterocycles, which are naturally occurring products, is very significant. A number of heterocyclic compounds, such as benzo-2-pyrones [1] and benzopyrazines [2,3] are found in natural systems.

Some of the substituted benzopyrazines (quinoxalines) have shown antibacterial [4] antifungal [5], anticancer [6], antitubercular [7] antileishmanial [8], and antimalarial activities [9]. For instance, actinomycin (Fig. 1), a substituted quinoxaline, inhibits the growth of gram positive bacteria and it is a blocking agent against various transplantable tumors [10]. Coumarin derivatives also possess diverse biological properties. For example, some polycyclic coumarins such as calanolides [11] isolated from *Calophyllum* genus, and others have shown potent anti-HIV activity [12]. Numerous coumarins have been also used as drug in contemporary medicine. As can be seen in Fig. 1, warfarin, acenocoumarol, and phenprocoumon are vitamin K antagonists which play anticoagulant role in treatment of thromboembolic disorders [13].

Besides, some coumarins are used as additive in food and cosmetics [14], optical brighteners [15], and dispersed fluorescent and laser dyes [16]. Based on these properties, the synthesis of these heterocycles has attracted much attention of researchers [17-20]. In this work, in regard of some reports on the application of manganese (II) sulfate monohydrate in organic transformations,

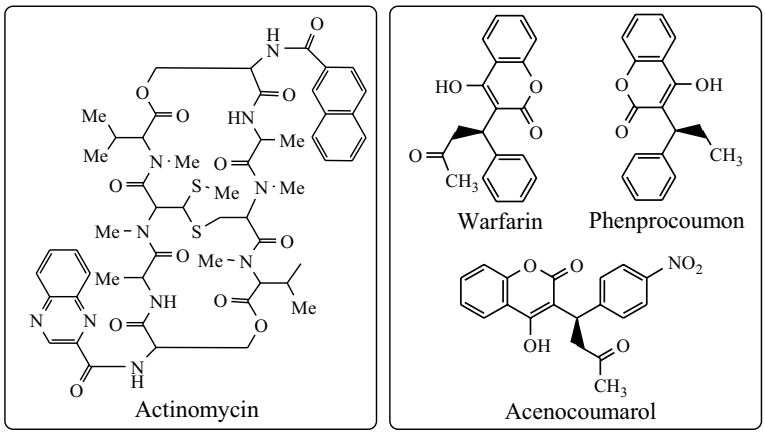

Fig. 1. Some biologically active coumarins and actinomycin.

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we decided to introduce a new application of manganese (II) sulfate monohydrate as a Lewis acid catalyst in synthesis of some benzo fused heterocycles containing nitrogen and oxygen atoms.

RESULTS AND DISCUSSION

Recently, heterogeneous catalysts have gained much attraction, because they are generally inexpensive, easily available and they can conveniently be handled and separated from the reaction mixture, thus the experimental procedure would be simple and eco-friendly [21]. Also, establishing the reaction based on solvent-free conditions obviously reduce pollution, and bring down handling costs due to simplification of experimental procedure, work up technique and saving in labour.

In 1883, Hans von Pechmann and Carl Duisberg found that phenols react with β-ketonic esters in the presence of sulfuric acid, giving coumarin (benzo-2-pyrone) derivatives [22]. Generally, Pechmann condensation reaction is common method for the synthesis of coumarin derivatives, because it needs simple precursors. In addition, coumarins with substitution on either pyrone or bezene ring or both are affordable in good to excellent yield via the Pechmann condensation. In this study, we found that the Pechmann cyclocondensation of phenols **1** with β-ketoesters **2** in the presence of $MnSO_4{\cdot}H_2O$ as an efficient catalyst produces the substituted coumarins **3** under thermal and solvent-free conditions (Scheme 1).

To make optimized conditions, the synthesis of compound 3a was chosen as a model. As shown in Table 1, it can be concluded that the thermal-assisted model reaction is efficiently carried out by adding catalytic amounts of $MnSO_4{\cdot}H_2O$ (20 mol%) in solvent-free conditions at 100 °C. It is noteworthy to not that in the absence of catalyst, the reaction didn't proceed for a long reaction time (12 h) and also using excessive amounts of catalyst cannot improve the product yield.

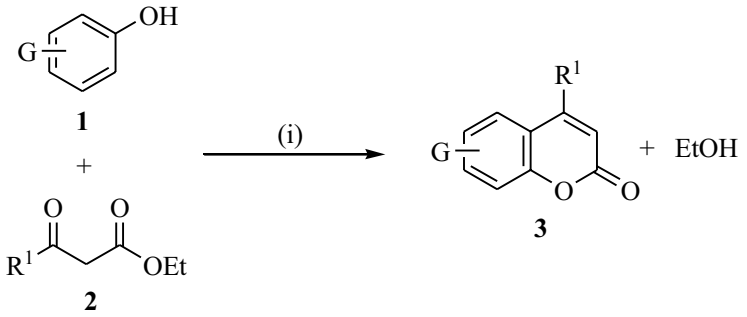
Table 1. The effect of catalyst amount on the synthesis of **3a** at 100^0C under solvent-free conditions.

Entry	Catalyst (mol%)	Time (min)	Yield [a] (%)
1	-	720	-
2	5	180	32
3	10	180	66
4	20	45	85
5	30	45	84

[a] Refers to isolated yields.

After optimization of the reaction conditions, various phenols such as resorcinol, pyrogallol and phloroglucinol were successfully used for the efficient Pechmann reaction (catalyzed by $MnSO_4{\cdot}H_2O$) with different β-ketoesters. A number of coumarins were obtained through this method in good yield and short reaction times (Table 2).

The ^{1}H NMR spectrum of **3a** exhibited five sharp singlets identified as methyl (δ = 2.49 ppm), olefinic pyrone ring (δ = 5.83 ppm) and two OH group (δ = 10.28, 10.51 ppm), protons. Two singlet signals (δ = 6.15 ppm) and (δ = 6.24 ppm) correspond to the aromatic protons of benzene ring. The proton decoupled ^{13}C NMR spectrum of **3a** showed 10 distinct resonances in accord with expected structure. A reasonable mechanism for manganese (II)-catalyzed Pechmann reaction has been proposed in Scheme 2.

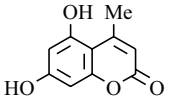
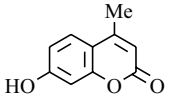
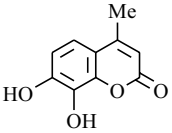
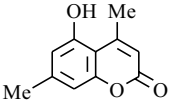
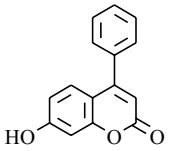
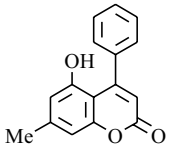
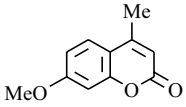


R:Me, Ph
G: H, OH, Me

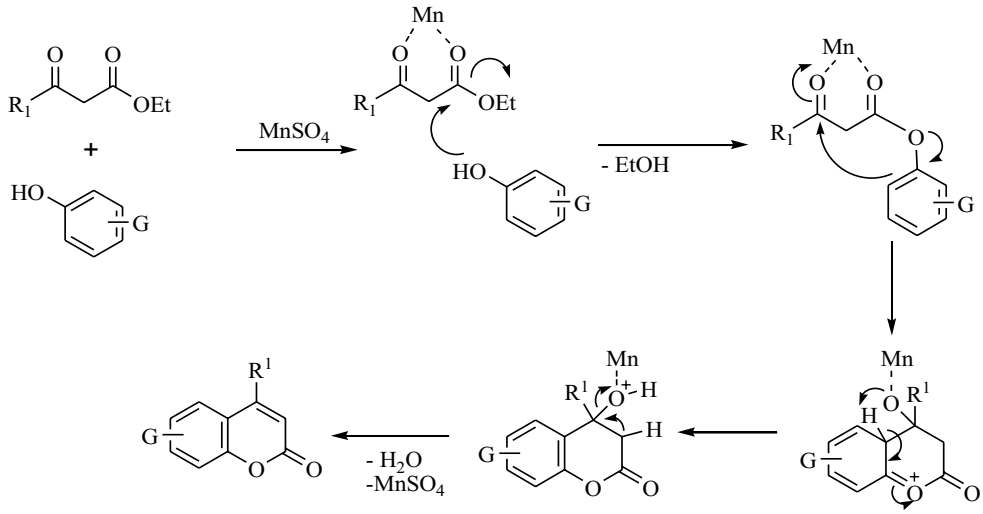
(i): $MnSO_4{\cdot}H_2O$ (20 mol%), solvent-free, 100 ^{o}C

Scheme 1. Pechmann condensation catalyzed by $MnSO_4{\cdot}H_2O$.

Table 2. Synthesis of some coumarin derivatives based on Pechmann condensation using $MnSO_4 \cdot H_2O$ at 100 °C under solvent-free conditions

Entry	Product	Time (min)	Yield (%)[a]	M.p. (°C)
3a		45	85	288-290
3b		60	80	188-190
3c		45	85	243-245
3d		60	90	244-246
3e		100	75	257-259
3f		90	80	243-245
3g		50	90	150-152

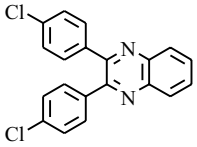
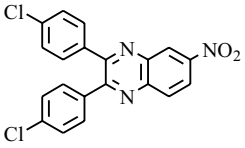
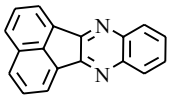
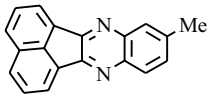
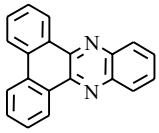
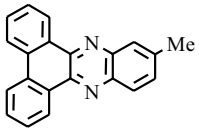
[a]Refers to isolated yields.



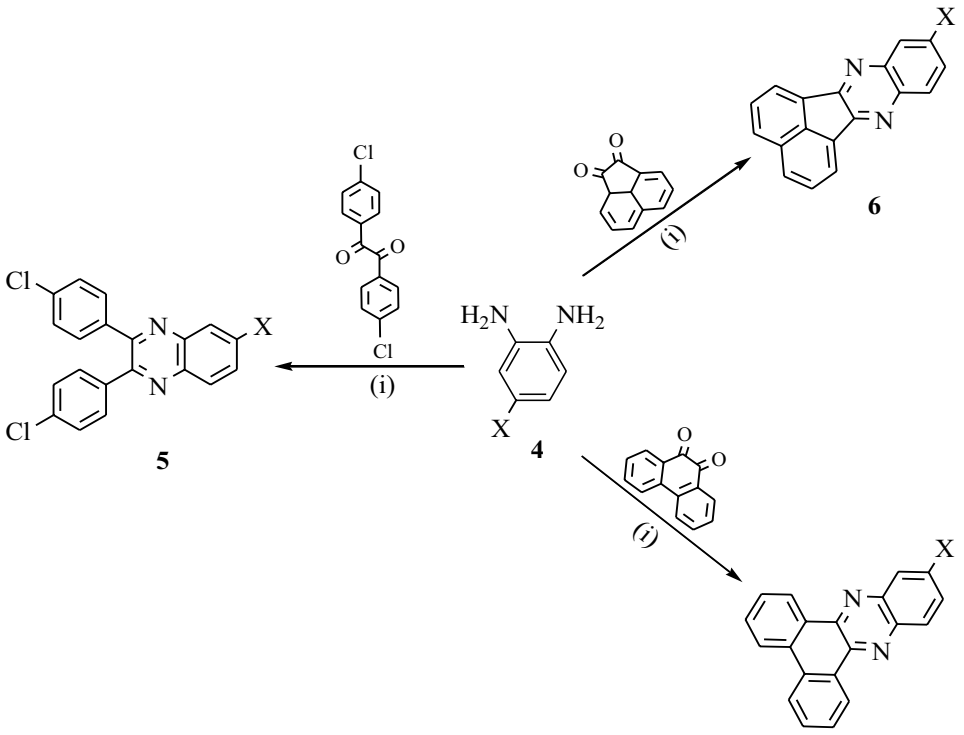
Scheme 2. Suggested mechanism for the Pechmann reaction catalyzed by $MnSO_4$.

This manganese (II)-catalyzed protocol was also applied for the condensation reactions involving the treatment of *o*-phenylenediamines **4** and three different aromatic 1,2-dicarbonyls to produce bezopyrazines (quinoxalines and phenazines) **5-7** in excellent yield. In this case, synthesis of 5a was selected as a model and after optimization through employing several amounts of catalyst, it was found that the results was satisfactory by adding $MnSO_4 \cdot H_2O$ (10 mol%) in EtOH at room

Table 3. Synthesis of benzopyrazine derivatives using $MnSO_4 \cdot H_2O$ in EtOH at room temperature

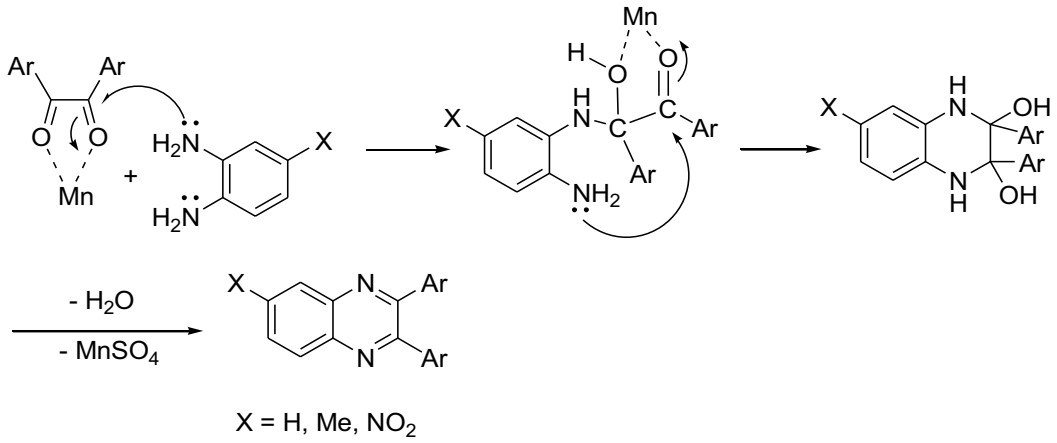
Entry	Product	Time (min)	Yield (%)[a]	M.p. (°C)
5a		35	95	192-194
5b		120	90	175-177
6a		15	90	238-240
6b		15	95	229-231
7a		12	98	225-227
7b		12	95	218-220

[a] Identified by comparison with authentic samples. [b] Refers to isolated yields.



(i): $MnSO_4.H_2O$ (10 mol%), EtOH, r.t.

Scheme 3. Synthesis of benzopyrazines by the use of $MnSO_4 \cdot H_2O$.



Scheme 4: Suggested mechanism for the synthesis of phenazines and quinoxalines using $MnSO_4$.

temperature (Scheme 3). Although the generally mechanistic details of this reaction are not yet fully understood, a feasible pathway depicted in Scheme 4. The driving force for all of these reactions is cyclo-aromatization. The catalyst has been applied successfully for the condensation of a variety of aromatic 1,2-dicarbonyl compounds with *o*-phenylenediamines. The results can be seen in Table 3.

It should be mentioned that the reaction of aliphatic 1,2-dicarbonyl compounds with *o*-phenylenediamines in the presence of this catalyst was unsuccessful and after a prolonged reaction time, the TLC of the reaction mixture showed a combination of starting materials and numerous products. It seems that the alkyle aldehydes are enolizable and it is a limiting factor.

EXPERIMENTAL

General

The chemicals were purchased from Merck, Fluka and Aldrich chemical companies. The reactions were monitored by TLC (silica-gel 60 F_{254}, hexane: EtOAc). IR spectra were recorded on a FT-IR Shimadzu-470 spectrometer and the ^{1}H NMR spectra was obtained on a Bruker-Instrument DPX-400 and 500 Avance 2 model.

*General procedure for the preparation of coumarin **3***

A mixture of phenol **1** (1 mmol), *β*-ketoesters **2** (1 mmol) and $MnSO_4{\cdot}H_2O$ (20 mol%) was stirred at 100 °C for an appropriate time. After completion of the reaction (controlled by TLC), the reaction mixture was cooled to room temperature and poured into crushed ice. Then, the precipitate was separated through simple filtration, washed with ice cold water. The pure product **3**, finally, was obtained after recrystallization from EtOH.

*Compound **3a**:* ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H), 10.28 (s, 1H), 6.24 (s, 1H), 6.15 (s, 1H), 5.83 (s, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.51, 160.55, 158.39, 155.43, 109.29, 102.55, 99.54, 94.98, 23.88. Anal. Calcd. For $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.69, H, 4.15.

*Compound **3b**:* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.47 (d, *J*=6.8 Hz), 6.85 (d, 1H, *J*=2 Hz), 6.82 (dd, 1H, *J*=6.8, 2.4 Hz), 6.14 (s, 1H), 5.7 (s, 1H), 2.35 (s, 3H). Anal. Calcd. For $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.36, H, 4.50.

Compound **3c:** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.15 (s, 1H), 9.30 (s, 1H), 7.08 (d, 1H, *J*=8.8 Hz), 6.81 (d, 1H, *J*=8.8 Hz), 6.10 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 160.47, 154.35, 149.81, 144.13, 143.74, 132.60, 115.88, 113.23, 112.56, 110.60, 40.42, 40.21, 40.00, 39.79, 39.58, 39.38, 39.17, 1863. Anal. Calcd. For $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.58, H, 4.27.

Compound **3d:** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 6.60 (d, 2H), 6.03 (s, 1H), 3.49 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 160.29, 156.90, 155.28, 155.04, 143.18, 112.37, 112.30, 108.15, 106.96, 23.91, 21.56. Anal. Calcd. For $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.71, H, 5.25.

Compound **3e:** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 7.34 (s, 4H), 7.28, (s, 2H), 7.05 (d, 1H, *J*=8.8 Hz), 6.56 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 161.80, 160.77, 155.96, 135.52, 130.07, 129.29, 128.79, 128.54, 113.68, 111.08, 110.70. Anal. Calcd. For $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.88, H, 4.18.

*Compound **3f*:** ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 7.37 (m, 5H), 6072 (s, 1H), 6.47 (s, 1H), 5.95 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 160.09, 156.05, 155.96, 155.91,

143.93, 139.75, 128.34, 127.92, 127.75, 113.88, 112.52, 108.19, 105.44, 21.65. Anal. Calcd. For $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.25, H, 4.82.

Compound ***3g*****:** ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 6.97 (s, 2H), 6.20 (s, 1H), 3.85 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.83, 160.59, 155.24, 153.86, 126.88, 113.66, 112.54, 111.58, 101.16, 56.36, 18.58. Anal. Calcd. For $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.70, H, 4.17.

General procedure for the preparation of benzopyrazines ***5-7***

A mixture of 1,2-dicarbonyl compound (1 mmol), *o*-phenylenediamine (1.1 mmol) and

$MnSO_4{\cdot}H_2O$ (10 mol%) in EtOH (5 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid was filtered and recrystallized from EtOH to afford the pure product **5-7**.

Compound **5a**: ^{1}H NMR (400 MHz, $CDC1_3$): δ 8.20 (m, 2H), 7.830 (m, 2H), 7.521 (m, 4H), 7.39 (m, 4H). ^{13}C NMR (500 MHz, $CDC1_3$): δ 152.34, 141.67, 137.69, 135.78, 131.61, 130.79, 129.63, 129.15. Anal. Calcd. For $C_{10}H_8O_4$: $C_{20}H_{12}Cl_2N_2$: C, 68.39; H, 3.44; N, 7.98. Found: C, 68.61; H, 3.40; N, 8.07.

Compound **5b**: ^{1}H NMR (400 MHz, $CDC1_3$): δ 9.08 (d, 1H, *J*=2.4 Hz), 8.58 (dd, 1H, *J*=9.2, 4 Hz), 8.33 (d, 1H, *J*=9.2 H), 7.57-7.54 (m, 4H), 7.43-7.30 (m, 4H). ^{13}C-NMR (100 MHz, $CDC1_3$): δ 155.18, 154.57, 148.53, 143.91, 140.40, 136.87, 136.72, 136.67, 136.60, 131.66, 131.58, 131.20, 129.37, 125.99, 124.08. Anal. Calcd. For $C_{20}H_{11}Cl_2N_3O_2$: C, 60.63; H, 2.80; N, 10.61. Found: C, 60.86; H, 2.70; N, 10.75.

Compound **6a:** ^{1}H NMR (400 MHz, $CDC1_3$): δ 8.21 (d, 2H, *J*=6.8 Hz), 8.02 (dd, 2H, *J*=6.2, 3.2 Hz), 7.90 (d, 2H, *J*=8.4 Hz), 7.65 (t, 2H, *J*=7 Hz), 7.57 (dd, 2H, *J*=6.4, 3.6 Hz); ^{13}C NMR (100 MHz, $CDC1_3$): δ 155.19, 142.39, 137.60, 132.92, 131.10, 130.47, 130.59, 130.36, 129.78, 122.96. Anal. Calcd. For $C_{18}H_{10}N_2$: C, 85.02; H, 3.96; N, 11.02. Found: C, 85.15; H, 3.90; N, 10.96.

Compound **6b**: ^{1}H NMR (400 MHz, $CDC1_3$): δ 8.21 (t, 2H, *J*=6.4 Hz), 7.90 (dd, 3H, *J*=8.2 Hz, 3.2 Hz), 7.79 (s, 1H), 7.64 (t, 2H, *J*=7.4 Hz), 7.40 (dd, 1H, *J*=8.4, 1.6 Hz), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDC1_3$): δ 155.15, 154.44, 142.38, 140.82, 140.71, 137.35, 133.08, 132.44, 131.06, 130.46, 130.31, 130.21, 129.89, 129.72, 122.83, 122.68, 22.94. Anal. Calcd. For $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44. Found: C, 85.24; H, 4.40; N, 10.12.

Compound **7a:** ^{1}H NMR (400 MHz, $CDC1_3$): δ 9.18 (d, 2H, *J*=7.6 Hz), 8.34 (d, 2H, *J*=8.0 Hz) 8.12 (dd, 2H, *J*=6.4, 3.6 Hz), 7.66-7.51 (m, 6H); ^{13}C NMR (100 MHz, $CDC1_3$): δ 143.54, 143.28, 133.15, 131.42, 130.88, 130.57, 129.04, 127.38, 124.03. Anal. Calcd. For $C_{20}H_{12}N_2$: C, 85.69; H, 4.31; N, 9.99. Found: C, 85.73; H, 4.33; N, 9.95.

Compound **7b**: ^{1}H NMR (400MHz, $CDC1_3$): δ 9.14 (dd, 2H, *J*=6.00, 1.6 Hz), 8.32 (2H, d, *J*=8 Hz), 7.97 (1H, d, *J*=8.4 Hz), 7.58 (s, 1H), 7.53-7.52 (m, 5H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDC1_3$): δ 143.29, 143.27, 142.72, 141.81, 141.41, 133.45, 133.06, 132.87, 131.49, 131.45, 131.20, 131.07, 130.01, 129.10, 128.92, 127.29, 127.15, 123.95, 23.20. Anal. Calcd. For $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.73; H, 4.75; N, 9.53

CONCLUSIONS

In summary, this study demonstrated the facile $MnSO_4{\cdot}H_2O$-catalyzed reactions with satisfactory results. Some important advantages of the presented methods are the short reaction time, high yields, simple workup procedures, and the use of inexpensive and available catalyst. These procedures do not involve any hazardous organic solvent, thus, they are they are environmentally friendly methods

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$MnSO_4.H_2O$: ВИСОКОЕФЕКТИВЕН И ЕВТИН КАТАЛИЗАТОР ЗА СИНТЕЗА НА БЕНЗО-2-ПИРОНИ И БЕНЗОПИРАЗИНИ

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(Резюме)

Предложена е ефективна и пряка методика за получаването на хетероциклени съединения като бензо-2-пирони и бензопиразини в присъствие на $MnSO_4 \cdot H_2O$ Като евтин катализатор. Тези нови методи са евтини и с предимства, Като отличен добив, използване на безопасен катализатор, достъпни реактиви и проста процедура.

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