Keggin Heteropolyacid Catalyzed Synthesis of Isoxazolo-[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones at Room Temperature

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Isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)diones **2a**—**2f** have been synthesized from the reaction of ethyl 5-amino-3-methyl-4-isoxazole carboxylate (**1**) with aryl isocyanates in the presence of Keggin heteropolyacid $H_3[PW_{12}O_{40}]$ as a green solid acid catalyst at room temperature in a one-pot process in good yields.

Keywords isoxazolopyrimidine, cyclization, heteropolyacid, Keggin, catalyst

Introduction

The purine base has been utilized to obtain biologically active compounds. The idea of modifying purine bases by replacing the imidazole ring with isoxazole to obtain the corresponding structure of isoxazolopyrimidine has been the subject of numerous studies.

Derivatives of isoxazolopyrimidine have significant biological activity and display analgesic,[1-3] anti-inflammatory,[4] bactericidal,[5-7] circulatory,[8] and anxiolytic activities.[9] Of the four structural isomers of isoxazolopyrimidines, only the isomer [5,4-*d*] has not been thoroughly investigated. To date, there have been only a few reports concerning the synthesis of derivatives of this isomer.[10-13] However, this synthesis has been usually carried out in polar organic solvents and with multi-step processes, without use of catalyst, in long reaction time. Therefore, improvements in such synthesis methods have been sought continuously. One of the important factors that can be improved besides the time and conditions of reaction, is catalyst, and along this line introduction of inexpensive and green catalysts with high acidity and excellent reusability is in much demand. Among various solid acids, heteropolyacids (HPA) have unique physical-chemical properties. Their acidity is significantly higher than those of traditional mineral acids. They have very strong Brønsted acidity approaching the superacid region and this acid-base property can be varied over a wide range by changing the chemical composition. Furthermore, they are capable of protonating and activating the substrate; and in some cases, they are more effective than usual inorganic acid and the traditional acid catalysts and can improve and reduce reaction time. Therefore, they are widely used as solid acid catalysts as green and eco-friendly catalysts in homogeneous and heterogeneous acid catalysis reactions for the synthetic reactions.[14]

Due to our interest in developing and improving green catalysts such as HPA,[15] and in continuation of our work with application of HPA to heterocyclization reactions,[16] in this article we wish to describe the synthesis of new derivatives of isoxazolo[5,4-*d*]pyrimidine **2a**—**2f** by use of heteropolyacid as solid acid catalyst. The novelty of this work lies in shorter time than earlier work, along with reusability new derivatives and greenness of the used catalyst.

Results and discussion

Recently, we described synthesis of new derivatives of heterocycles by HPA instead of mineral acids like HCl or H_2SO_4 as eco-friendly catalysts.[16] Therefore, it was a great interest to continue our investigations on other reactions. We selected **1** and aryl isocyanates as starting materials and Keggin HPA as catalyst which is low in toxicity, highly stable towards humidity, air stable and is very well documented in green chemistry.

When a mixture of **1** and aryl isocyanates in acetic acid was stirred at room temperature in the presence of a catalytic amount of $H_3[PW_{12}O_{40}]$, during 1.5—2 h, cyclization occurred and compounds **2a**—**2f** were obtained [Eq. (1)]. The results are shown in Table1. The synthesis of **2a**—**2f** was investigated, using various solvents, such as hexane, chloroform, xylene, dioxane, toluene and acetic acid at room temperature and reflux conditions. We found out that acetic acid was the most effective solvent for making the reaction faster and giving the best yields. It is also noteworthy to mention that mixing of the reactants in acetic acid without any catalyst did not give any good yields even in prolonged re-

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action time.

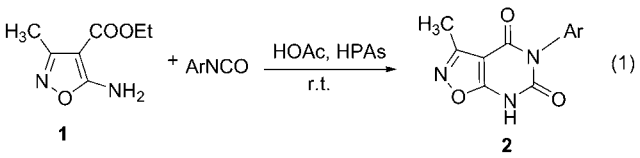

Table 1 Catalytic synthesis of isoxasolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones

Compd.	Ar	Yield/%	m.p./℃
2a	C_6H_5	65	210—212
2b	4-MeC_6H_4	76	202—204
2c	3-MeC_6H_4	70	205—206
2d	3-ClC_6H_4	73	250—252
2e	3,4-$Cl_2C_6H_3$	46	272—274
2f	4-$NO_2C_6H_4$	46	176—178

Reusability of catalyst

An important advantage of this catalyst is the ease of separating it from the reaction mixture, as well as the fact that it could be recycled a number of times. In our studies it has been found that the used catalyst catalyzed the reaction without any degradation of structure. This leads to the recovery and recycling of the catalyst, which is very important in catalytic processes, especially, in industry. Recovery has decreased the catalytic activity by only 2%—4%.

Experimental

Chemicals and apparatus

All of the chemicals were obtained from commercial sources and used as received. All yields were calculated from crystallized products. IR spectra were obtained on a Brucker 500 scientific spectrometer. ^{1}H NMR spectra were recorded on an FT NMR Bruker 100 MHz Aspect 3000 spectrometer. Mass spectra were recorded on an MS5973 Network Mass Selective detector. Melting points were obtained on an Electrothermal type 9100 apparatus.

Ethyl 5-amino-3-methyl-4-isoxazole carboxylate (1)

A mixture of ethyl cyanoacetate (7 mmol), and triethyl orthoacetate (7.7 mmol) in acetic anhydride (5 mL) was refluxed with stirring for 3 h. After cooling, the reaction mixture was filtrated. The solid product (ethyl 2-cyano-3-ethoxy-2-butenoate) was collected, dried and crystallized from MeOH. Yield 75%, m.p. 42—44 ℃. Then to a mixture of hydroxylamine hydrochloride (1 mmol) in solution of 10% NaOH (5 mL) was added ethyl 2-cyano-3-ethoxy-2-butenoate (1 mmol) and the resulting mixture was refluxed with stirring. The progress of reaction was monitored by TLC. After 3 h, the reaction was completed. After cooling, the reaction mixture was filtrated. The solid residue was then washed with acetone and the solvent evaporated to give the crude product (75%), m.p. 133—135 ℃. The solid product was ethyl 5-amino-3-methyl-4-isoxazole carboxylate (**1**).

Isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones 2a—2f

To a mixture of ethyl 5-amino-3-methyl-4-isoxazole carboxylate (1 mmol) in acetic acid (5—7 mL) with stirring and during 10 min at room temperature, were added aryl isocyanat (1 mmol) and then $H_3[PW_{12}O_{40}]$ (0.06 g, 0.02 mmol). The progress of the reaction was monitored by TLC. Then the reaction mixture was filtered to give the product. For further purification, it was crystallized from n-hexane to afford the pure products **2a**—**2f**.

2a: ^{1}H NMR (DMSO-d_6) δ: 8.55 (s, NH, 1H), 7.11—7.65 (m, phenyl ring, 5H), 2.08 (s, CH_3-isoxazol ring, 3H); ^{13}C NMR (DMSO-d_6) δ: 158.6 (amid carbonyl), 98.2—155.6 (isoxazole ring), 149.8 (urea carbonyl), 128.1—136.3 (phenyl ring), 12.5 (CH_3-isoxazol ring); MS *m*/*z*: 243 (M^+).

2b: ^{1}H NMR (DMSO-d_6) δ: 8.39 (s, NH, 1H) 7.04—7.54 (dd, phenyl ring, 4H), 2.21 (s, CH_3-isoxazol ring, 3H) 1.90 (s, CH_3-phenyl ring, 3H); ^{13}C NMR (DMSO-d_6) δ: 153.4 (amid carbonyl), 102.7—159.1 (isoxazole ring), 143.3 (urea carbonyl), 129.7—137.7 (phenyl ring), 22.6 (CH_3-phenyl ring), 11.8 (CH_3-isoxazol ring); MS *m*/*z*: 257 (M^+).

2c: ^{1}H NMR (DMSO-d_6) δ: 8.6 (s, 1H, NH), 7.08—7.52 (m, 4H, phenyl ring), 2.15 (s, 3H, CH_3-isoxazol ring) 1.84 (s, 3H, CH_3-phenyl ring); ^{13}C NMR (DMSO-d_6) δ: 159.4 (amid carbonyl), 95.2—147.6 (isoxazole ring), 150.7 (urea carbonyl), 126.3—139.5 (phenyl ring), 27.2 (CH_3-phenyl ring), 14.5 (CH_3-isoxazol ring); MS *m*/*z*: 257 (M^+).

2d: ^{1}H NMR (DMSO-d_6) δ: 8.64 (s, 1H, NH), 7.12—7.58 (m, 4H, phenyl ring), 2.22 (s, 3H, CH_3-isoxazol ring); ^{13}C NMR (DMSO-d_6) δ: 161.2 (amid carbonyl), 106.2—151.9 (isoxazole ring), 144.1 (urea carbonyl), 122.1—138.3 (phenyl ring), 15.8 (CH_3-isoxazol ring); MS *m*/*z*: 277 (M^+), 279 (M^++2).

2e: ^{1}H NMR (DMSO-d_6) δ: 9.01 (s, 1H, NH), 7.23—7.68 (m, 3H, phenyl ring), 2.13 (s, 3H, CH_3-isoxazol ring); ^{13}C NMR (DMSO-d_6) δ: 154.3 (amid carbonyl), 96.6—157.2 (isoxazole ring), 151.8 (urea carbonyl), 125.1—139.3 (phenyl ring), 12.5 (CH_3-isoxazol ring); MS *m*/*z*: 311 (M^+), 313 (M^++2), 315 (M^++4).

2f: ^{1}H NMR (DMSO-d_6) δ: 8.83 (s, 1H, NH), 7.11—7.95 (dd, 4H, phenyl ring), 2.23 (s, 3H, CH_3-isoxazol ring); ^{13}C NMR (DMSO-d_6) δ: 153.6 (amid carbonyl), 107.1—152.4 (isoxazole ring), 152.8 (urea carbonyl), 124.7—145.3 (phenyl ring), 17.7 (CH_3-isoxazol ring); MS *m*/*z*: 288 (M^+).

Conclusion

A facile and green procedure for the syntheses of **2a—2e** is realized in the presence of $H_3[PW_{12}O_{40}]$ in short time. This Keggin type catalyst is inexpensive, eco-friendly and recyclable, which can be used for the synthesis of other heterocyclic compounds.

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