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Application of $[MeC(OH)_2]^+ClO_4^-$ super acidic ionic liquid as highly efficient catalyst for multi-component synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones

Behrooz Mirza

Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran

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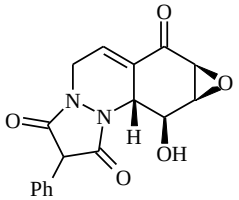
Abstract: $[MeC(OH)_2]^+ClO_4^-$ as a super acidic ionic liquid is found to be a highly efficient catalyst in the synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones derivatives via three-component condensation of aromatic aldehyde, malononitrile, and 4-phenylurazole in solvent-free conditions. The turn over frequency (TOF) values of the catalysts are higher than some of the previously reported catalysts.

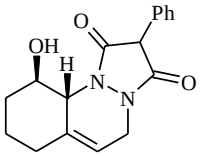
Keywords: Ionic liquid, Malononitrile, Pyrazolo[1,2-a][1,2,4]triazole-1,3-diones, Super acidic.

Introduction

Multicomponent reactions (MCRs) are generally defined as reactions where more than two starting materials react to form a product. Generally, there are three different possible classification schemes of MCRs according to reaction mechanism, components involved, or intrinsic variability [1]. The development of new MCRs is an interesting research topic in applied areas of organic, medicinal, and pharmaceutical chemistry [2]. MCRs have attracted considerable
interest owing to their exceptional synthetic efficiency. Hundreds of MCRs have recently been described. These reactions play a pivotal role in the synthesis of natural and unnatural products because of their importance of therapeutic and pharmacological uses.
Economical ionic liquids are important in the organic synthesis, which could effectively drive the development of green and chemical industries.
As is known to all, discovering a new ionic liquid is relatively easy, but determining its usefulness as a solvent and catalyst requires a much more substantial investment [3–7]. *N*-Heterocycles receive considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores [8]. Among a large variety of *N*-containing heterocyclic compounds, those containing Pyrazoles or urazole (1,2,4-triazolidine-3,5-dione) moiety have received considerable attention because of their pharmacological properties and clinical applications [9-12] (Figure **1**).



inhibitor of HSP induction



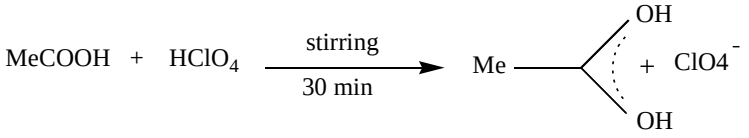
antimicrobial agent

Recently, Tamaddon *et al.* reported an efficient protocol for the preparation of heterocyclic compound by employing a super acidic ionic liquid $[MeC(OH)_2]^+ClO_4^-$ [13]. The super acid was readily

*Corresponding author. Tel: 02422273425, Fax: +98 (413) 4327501, E-mail: b.mirza@kiau.ac.ir

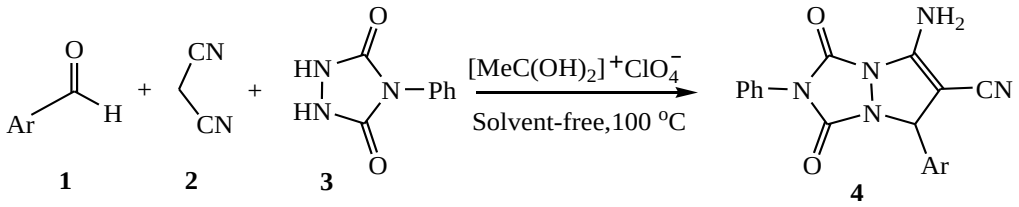
prepared by mixing acetic acid and perchloric acid at room temperature, while showing a strong protonation ability even for very weak organic bases (pH = –4.4) (Scheme **1**) [14,15].

We envisioned that this acidic room-temperature ionic liquid should be a good catalyst for synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones derivatives (Scheme **1**) .



Scheme 1: Preparation of super acidic ionic liquid

Herein we report a convenient and facile one pot method for the synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones **4** via three-component reaction between aromatic aldehydes **1** , malononitrile **2** and 4-phenylurazole **3** in the present of $[MeC(OH)_2]^+ClO_4^-$ as a super acidic catalyst under solvent-free condition (Scheme **2**).



Scheme 2: Synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones via three-component reaction between aromatic aldehydes 1 , malononitrile 2 and 4-phenylurazole 3 in the present of $[MeC(OH)_2]^+ClO_4^-$**.**

Results and discussion

At first, for the optimization of the reaction conditions, the model reaction was carried out by using 4-phenylurazole, 4-chlorobenzaldehyde, and malononitrile under various conditions.

The reaction was conducted in various solvents using $[MeC(OH)_2]^+ClO_4^-$ as a catalyst under refluxing conditions and also under solvent-free conditions. As can be seen from Table **1**, the best results were obtained in neat. The effect of temperature in solvent-free conditions was studied by carrying out the reaction at 80, 100, and 120°C. The results from Table **1** (entry 5) showed that 100°C would be the best temperature for all reactions. However, only a trace amount of the product was formed in the absence of catalyst (Table **1**, entry 1). Then, optimization of catalyst amounts was carried out in the model study by using different amounts of the $[MeC(OH)_2]^+ClO_4^-$. The higher yield was obtained with increasing the amount of catalyst from 1 mol% to 2 mol%. No substantial improvement in the yield was observed by increasing the amount of $[MeC(OH)_2]^+ClO_4^-$ to 5 mol%. (Table **1**). Finally, it was found that the reaction gave satisfying result in the presence of $[MeC(OH)_2]^+ClO_4^-$ (2mol%) at 100 °C under solvent-free conditions. The efficacy of our protocol was well evaluated using a wide range of aldehydes.

As indicated in Table **2**, it seemed that there was no remarkable electronic effect from the substituents on aldehyde moiety, since the aryl aldehydes with both electron-donating and electron-withdrawing groups could be applied as efficient candidates for the synthesis of corresponding pyrazolo[1,2-a][1,2,4]triazole-1,3-diones derivatives in good yields. However, the aliphatic aldehydes such as butanal or pentanal reacted slowly as compared to the aryl aldehydes and gave low yields of the products (Table **2**).

The compounds **4a**–**j** were known compounds and their identity was confirmed by a comparison of their m.p. (Table **2**) and their spectral properties with literature data [16-20].

To compare the applicability and efficiency of $[MeC(OH)_2]^+ClO_4^-$ with reported catalysts in the synthesis of 7-amino-5-(4-chlorophenyl)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-6-carbonitrile, we have tabulated the turn over frequency (TOF), of these catalysts in the condensation reaction of 4-phenylurazole, 4-chlorobenzaldehyde, and malononitrile (Table **3**). As shown in Table **3**, $[MeC(OH)_2]^+ClO_4^-$ relative to the previously reported catalysts, is superior in terms of TOF.

Table 1: Reaction of 4-phenylurazole, 4-chlorobenzaldehyde and malononitrile under different conditions[a]

Entry	Catalyst(mol%)	Solvent	Temp(^{0}C)	Time(min)	Yield(%)[b]
1	-	-	120	100	trace
2	AcOH(20)	-	120	60	35
3	$HClO_4$ (20)	-	120	60	40
4	$[MeC(OH)_2]^+ClO_4^-$(1)	-	100	40	70
5	$[MeC(OH)_2]^+ClO_4^-$(2)	-	100	40	95
6	$[MeC(OH)_2]^+ClO_4^-$(3)	-	100	40	95
7	$[MeC(OH)_2]^+ClO_4^-$(4)	-	100	40	90
8	$[MeC(OH)_2]^+ClO_4^-$(5)	-	100	40	85
9	$[MeC(OH)_2]^+ClO_4^-$(2)	-	80	40	75
10	$[MeC(OH)_2]^+ClO_4^-$(2)	-	120	40	95
11	$[MeC(OH)_2]^+ClO_4^-$(2)	-	rt	70	60
12	$[MeC(OH)_2]^+ClO_4^-$(2)	ETOH	Reflux	60	80
13	$[MeC(OH)_2]^+ClO_4^-$(2)	CH_3CN	Reflux	60	75
14	$[MeC(OH)_2]^+ClO_4^-$(2)	ETOAc	Reflux	60	85

[a] Reaction conditions: malononitrile (1 mmol), 4-phenylurazole (1 mmol), aromatic aldehydes (1 mmol); catalyst: $[MeC(OH)_2]^+ClO_4^-$ (2 mol%); temp: 100 °C; solvent free. [b] Isolated yields.

Table 2. Three-component reaction of malononitrile,4-phenylurazole and aromatic aldehydes catalyzed by $[MeC(OH)_2]^+ClO_4^-$ under solvent-free conditions[a]

Entry	**Ar**	**Time(min)**	**Yield[b] (%)**	**M.P. (°C)**	**mp[lit] (°C)**
4a	4-NO_2-C_6H_4	35	92	>220	>218[(16-20)]
4b	2-Cl-C_6H_4	40	86	>222	>218[(16-20)]
4c	C_6H_5	40	90	>217	>210[(16-20)]
4d	4-Cl-C_6H_4	40	95	>223	>221[(16-20)]
4e	2-NO_2-C_6H_4	40	85	>230	>221[(16-20)]
4f	4-Br-C_6H_4	40	90	>227	>224[(16-20)]
4g	4-Me-C_6H_4	45	82	>221	>217[(16-20)]
4h	2,4-Cl-C_6H_3	35	90	>215	>200[(16-20)]
4i	3-CN-C_6H_4	35	87	>226	>225[(16-20)]

4j	4-F-C_6H_3	35	90	>227	>222[16-20]
4k	C_2H_5	50	-	-	-

[a] Reaction conditions: malononitrile (1 mmol), 4-phenylurazole (1 mmol), aromatic aldehydes (1 mmol); catalyst: $[MeC(OH)_2]^+ClO_4^-$ (2 mol%); temp: 100 °C; solvent free. [b] Isolated yields.

Table 3: Comparison of the results of the reaction of 4-phenylurazole , 4-chlorobenzaldehyde, and malononitrile using $[MeC(OH)_2]^+ClO_4^-$ with those obtained by reported catalysts.

Catalyst/conditions	Catalyst amount (mol%)	Time (min)	Yield[a] (%)	TOF[b] (min^{-1})	Ref.
Et_3N /EtOH/50°C, ultrasound	20	30	91	0.15	16
DABCO /EtOH/50°C, ultrasound	20	20	95	0.23	20
Nano-ZrO_2, solvent free, 100 °C	20	30	90	0.15	15
Nano-ZnO, solvent free, 80 °C	15	25	88	0.23	19
N-Butyl-N-methlpyrrolidinium acetate, solvent free 80 °C	15	10	94	0.62	18
1-Ethyl-3-methylimidazolium Acetate, solvent free 80 °C	15	15	93	0.4	18
$[MeC(OH)_2]^+ClO_4^-$, solvent free 100 °C	2	40	95	1.18	Present work

[a] Isolated yield,
[b] Turn over frequency.

Experimental

Apparatus and analysis:

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Typical procedure for the synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones:

A mixture of malononitrile (1.0 mmol), aromatic aldehyde (1.0 mmol), 4-arylurazole (1.0 mmol), and $[MeC(OH)_2]^+ClO_4^-$ (0.02 mmol) was heated at 100°C for 35-45 min. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. The solid residue was dissolved in water to separate the catalyst and wash with diethylether. By recrystallization from ethanol, pure products were obtained.

Selected spectral data:

7-amino-5-(4-chlorophenyl)-1,2,3,5-tetrahydro-1,3-dioxo-2-phenylpyrazolo[1,2-a][1,2,4]triazole-6-carbonitrile **4a**:

White powder mp >223 ºC, yield 95%, IR (KBr) (ν_{max}, cm^{-1}):1731, 1712 (CO ester), ^1H NMR (500 MH_Z, DMSO-d_6): δ = 6.03 (1H, s, CH), 7.35-8.35 (11H, m, *H*-Ar and NH_2). ^{13}C NMR (125.8 MH_Z, DMSO-d_6): δ = 61.7, 63.6, ,116.4, 124.2, 126.7, 128.4,

128.8, 129.2, 129.7, 130.3, 131.0, 131.8, 146.3, 148.0, 150. 7,154. Analyses: Calcd. for $C_{18}H_{12}ClN_5O_2$: C, 59.11; H, 3.31;N, 19.15 Found: C, 59.34; H, 3.12;N, 19.36 %.

Conclusion

In conclusion, we have demonstrated that $[MeC(OH)_2]^+ClO_4^-$ can be used as super acidic ionic liquid catalyst for efficient synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones derivatives under solvent-free conditions. Moreover, the cheapness, easy availability of the reagent, high yield, purity of the products easy and clean workup and higher turn over frequency (TOF) of the catalyst in comparison with reported catalysts are some important advantages presented in this work.

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References

[1] Zhu, J.; Bienayme, H. Multicomponent Reactions; Wiley: Weinheim, Germany, **2005**.
[2] Tietze, L.F. *Chem. Rev*., **1996**, 96, 115.
[3] Kirchner, B. Ionic Liquids; Springer: *New York*, USA, **2009**.
[4] Sanjay, M.V. Ionic Liquids in Synthesis; Wiley-VCH: Oxford, United Kingdom, **2008**.
[5] Wasserscheid, P.; Welton, T. Ionic Liquids in Synthesis; Wiley-VCH: Weinheim, Germany, **2008**.
[6] Hajipour, A.R.; Rafiee, F. *J. Iranian Chem. Soc.*, **2009**, 6, 647.
[7] Marcos, A.P.M.; Clarissa, P.F.; Dayse, N.M.; Nilo, Z.; Helio, G.B. *Chem. Rev*., **2008**, 108, 2015.
[8] Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katriztky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Elsevier: Oxford, **1996**, 207.
[9] Boatman, P.D.; Urban, J.; Nguyen, M.; Qabar M.; Kahn. M. *Bioorg. Med. Chem. Lett.*, **2003**,13, 1445.
[10] Izydore, R. A. ; Bernal-Ramirez, J. A.; Singh, P. *J. Org. Chem.*, **1990**, 55, 3761.
[11] Kiriazis, A.; Ruffer, T.; Jantti , S.; Lang, H.; Yli-Kauhaluama, J. *J. Comb. Chem*., **2007**, 9, 263.
[12] Kolb, V. M.; Dworkin, J. P.; Miller, S. L. *J. Mol. E.*,**1994**, 38, 549.
[13] Tamaddon, F.; Bistgani, J. M. *Synlett*, **2011,** 2947.
[14] Hall , N. F.; Conant, J. B. *J. Am. Chem. Soc.*, **1927**, 49, 3047.
[15] Conant, J. B.; N.F. Hall, *J. Am. Chem. Soc.*, **1927**, 49, 3062.
[16] Azarifar, D.; Yami, R. N.; *Heterocycles,* **2010**, 81, 2063.
[17] Shaterian , H. R.; Moradi, F. *Research on Chemical Intermediates*, **2015** ,1, 223.
[18] Shaterian, H. R.; Azizi, K. *Journal of Molecular Liquids*, **2013**, 83, 8.
[25] Azarifar, A.; Nejat- yami, R.; Azarifar, D. *J. Iran. Chem. Soc.*, **2013**,10, 297.
[26] Azarifar, D.; Nejat-Yami, R.;. Zolfigol, M. A. *J. Heterocyclic Chem*., **2013**,1386, 50.