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A Rapid and Efficient one Pot Synthesis of Imidazole Derivative

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Introduction

Imidazole compounds are an important class of five-membered nitrogen heterocyclic compounds that have attracted much attention because they share the structure of biological products such as histidine, histamine and biotin [1]. Part of imidazole is the main structure for the synthesis of many important drugs such as losartan, olmesartan, eprosartan and tripingretin.

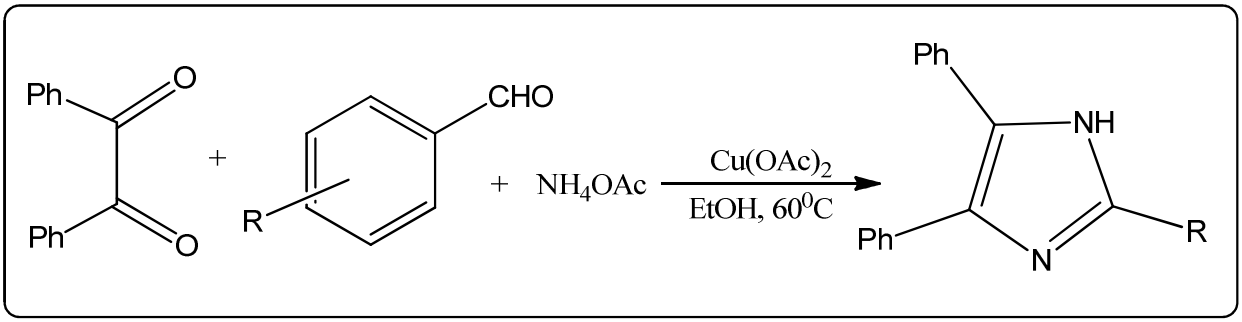
Multicomponent reaction (MCR) plays an vital role in combinatorial chemistry because it enables the synthesis of target compounds with better efficiency and atom economy by forming a complex process with three or more reactants in one step. Product yield and reaction time are very important in organic synthesis. The increase in reaction step results in a decrease in the final product yield and an increase in the total reaction time. Multicomponent reactions help solve this problem. Multicomponent reactions (MCRs) have become a useful and powerful tool in modern synthesis because complex organic molecules can be quickly, rapidly and efficiently constructed from simple and readily available substrates without the need to separate intermediates [3,4]. The imidazole moiety is present in many natural molecules and pharmaceutically active compounds [5,6]. Among them, polysubstituted imidazoles have attracted attention due to their chemical and biological activities such as anticancer [7,8] and anticoagulant [9], anti-inflammatory [10], antibacterial and antifungal [11,12], antituberculosis [13], antiepileptic [14], anticonvulsant [15]. Over the past few years, various methods have been developed for the synthesis of substituted imidazoles using various catalytic systems. Methods using ultrasonic energy [16], acid [17], and supported catalysts [18] are also described. However, most of the methods reported above have one or more disadvantages, such as the use of expensive metal reagents, long reaction times, and laborious separation.

Experimental:

All precursor were purchased from Merck and used without further purification. All chemicals are commercially available and used without the need for further filtration. Melting points are indicated in open capillaries and are not constant. All solvents were purified and dried by standard methods before use. The combination was confirmed by TLC.

General procedure for the synthesis of Imidazole derivatives:

Bezil (1 mmol), aromatic aldehyde (1 mmol) and ammonium acetate (2 mmol) in a bucket-bottom flask with 10 mol% $Cu(OAc)_2$ ethanol solution (10 mL). . The reaction mixture was then stirred at 60°C for the appropriate time, monitored by TLC. After the reaction is completed. The progress of the reaction was monitored using TLC. After the reaction is complete, the mixture is poured onto crushed ice and the resulting precipitate is filtered, dried and purified using ethanol.



Result and Discussion:

Optimization of reaction condition for the synthesis of imidazole derivative from aromatic aldehyde, benzile and ammonium acetate at 60°C carried out at an different attempt to find out ideal condition for the synthesis. At the beginning of synthesis reaction was proceeded using 2.5 mol% $Cu(OAc)_2$ as an catalyst but only trace amount of product was observed (entry 1). Moreover the concentration of catalyst was increased from 5 mol% and 7.5 mol% under solvent free condition in a separate attempt for 12 hr. to product 28% and 45% of imidazole derivative respectively (entry 2-3).

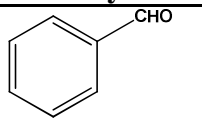
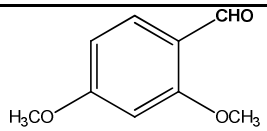
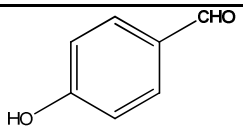
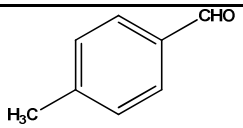
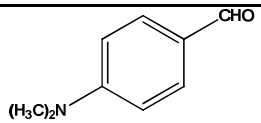
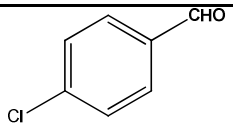
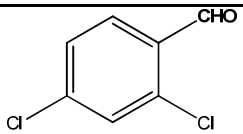
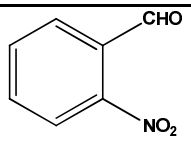
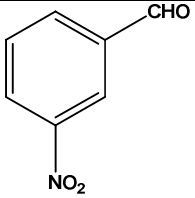
Table 1: Optimization of reaction condition for the synthesis of Imidazole derivative.

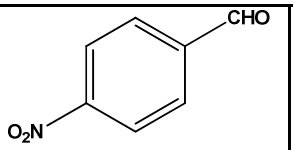
Entry	Catalyst (mol%)	Solvent	Time	Yield (%)
1	2.5	-	24	Trace
2	5	-	12	28
3	7.5	-	12	45
4	10	-	06	54
5	12.5	-	06	55
6	15	-	06	58
7	10	EtOH	4	82
8	10	MeOH	5	74
9	10	C_6H_6	6	65
10	10	CH_2Cl_2	6	62

In a next attempt the of experiment the concentration of catalyst was taken 10 mol% , 12.5 mol% and 15 mol% for the synthesis of imidazole derivative from aromatic aldehyde, benzil and ammoinium acetate so it generate 54%, 55% and 58% of product respectively (entry 4-6). From this observation it was concluded that 10 mol% of catalyst produces good yield with minimum amount of catalyst so it was considered to be an standard amount of catalyst for the synthesis of imidazole derivative but yield of entry 4 was not still enough to proceed for further synthesis. So in next part of research solvent effect was taken into account. Following the same protocol for the synthesis of imidazole derivative using ethanol and methanol as a solvent in different attempt provides an astonishing result with 82% and 74%

of yield within 4hr to 5 hr respectively (entry 7-8). This result surprisingly shows that effect of solvent shows enhanced yield of corresponding product. At the end of practice synthesis was performed with benzene and dichloromethane as a solvent afford an unsatisfied yield of 65% and 62% respectively (entry 9-10). From the whole series of experiment it was concluded that aromatic aldedyde, benzil and ammonium acetate undergoes reaction with 10 mol% of copper acetate with ethyl alcohol as a solvent at 60 ^{0}C considered as ideal condition.

Table 2: Optimization of isolated yield of product at standard condition.

Entry	Aldehyde	Time	Yield (%)	M.P.
1		**4**	**82**	218-220
2		**5**	**73**	164-165
3		**5**	**76**	232-233
4		**6**	**68**	184-186
5		**6**	**63**	260-261
6		**3.5**	**86**	262-264
7		**4**	**84**	174-176
8		**3**	**92**	230-233
9		**3.5**	**86**	145-147

10		**3**	**89**	242

In next part of the research the yield of the product is elucidated under standard condition. Also the effect of electron donating and electron withdrawing group on yield of the product is determined. As seen from the table benzldehyde was allowed to react with benzil and ammonium actetate gives 82% of yield (entry 1). Morevever the benzaldehyde containing electron donating group such as 2,4 dimethoxybenzaldehyde, 4-hydroxybenzaldehyde, 4-methylbenzaldehyde and N,N dimethyl benzaldehyde under ideal condition described above generate 73%, 76%, 68% and 63% yield respectively (entry 2-5).

Moving further the effect of electron withdrawing group on amount of product was studied by taking 2-chloro benzaldehyde, 4-chloro benzaldehyde , 2-nirobenzaldehyde, 3-nitrobenzaldehyde and 4-nitro benzaldehyde in separate attempt of synthesis for imidazole derivative from aromatic aldehyde, benzil and ammonium acetate using copper acetate as catalyst produces 86%, 84%, 92%, 86% and 89% respectively (entry 6-10). It is clear from the data that electron withdrawing group increases yield of corresponding product.

Conclusion:

Effective and efficient procdedure for the synthesis of imidiole derivative from aromatic aldehyde, benzil and ammonium acetate mediated by copper acetate as a catalyst give good to excellent yield which is in the range from 73% to 92%. The present protocol proceed very smoothly the catalyst is isolated easily at the end of reaction which provides an shorter route with reducing activation energy complete the present protocol within a short of time.

References:

1. S. A. Laufer, W. Zimmermann, K. J. Ruff, *J. Med. Chem.*, **47**, 6311(2004).
2. C. Leister, Y. Wang, Z Zhao, C. W. Lindsley, *Org. Lett.*, 6, 1453 (2004).
3. D. Strubing, H. Neumann, S. Klaus, S. Hubner, *Tetrahedron,* **61**, 11333 (2005).
4. L. Yu, B. Chen, X. Huang, *Tetrahedron Lett.,* **48**, 925 (2007).
5. J. Z. Ho, R. M. Hohareb, J. H. Ahn, T. B. Sim, H. Rapoport, *J. Org. Chem*., **68**, 109 (2003).
6. J. G. Lombardino, E. H. Wiseman, *J. Med. Chem.*, **17**, 1182 (1974).
7. I. Ali, M. N. Lone, H. Y. Aboul-Enein, *Med. Chem. Commun*., **8**, 1742(2017).
8. S.Baroniya, Z. Anwer, P. K.Sharma, R. Dudhe, N. Kumar, *Der Pharm Sin,* **1**, 172(2010).
9. M. R. Wiley, L. C. Weir, S. L. Briggs, N. Y. Chirgadze, D. Clawson, *Bioorg. Med. Chem. Lett.,* **9** 2767 (1999).
10. A. Puratchikodya, M. Doble, *Bioorg. Med. Chem*., **15,** 1083(2007).
11. K. C. S. Achar, K. M. Hosamani, H. R. Seetharamareddy, *Eur. J. Med. Chem.,* **45**, 2048 (2010).
12. D. Sharma, B. Narasimhan, P. Kumar, *Eur. J. Med. Chem.,* **44,** 2347(2009).
13. J. Pandey, T. K. Vinod, S.S. Verma, *Eur. J. Med. Chem.,* **44,** 3350(2009).
14. R. Mishra, S. Ganguly, *Med Chem Res*, **21**, 3929(2012).
15. D. W .Robertson, E. E. Beedle, R. Lawson, J. D. Leander, *J Med Chem,* **30**,939(1987).
16. Z. Hongjun, S. Qiuhong, M. Yingming, C. Bo-Wen and J. Song, Ultrason. Sonochem., **17**, 749(2010).
17. L. Nagarapu, S. Apuri, S. Kantevari, *J. Mol. Catal. A: Chem.*,**266**, 104(2007).
18. L. Wang, C. Cai, *Monatsh. Chem*., **140**, 541(2009).

