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An Efficient and Convenient Synthesis of 1H-Pyrazolo [1, 2-b] Phthalazine-5, 10-Dione Derivatives Mediated by L-Proline

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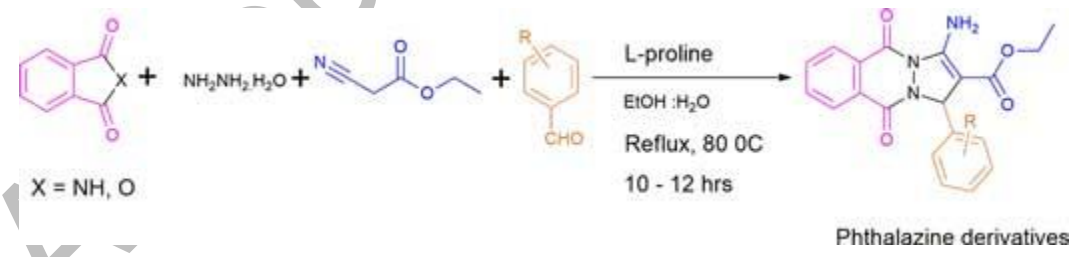
Abstract

An efficient, four-component, one-pot condensation reaction among phthalimide or phthalic anhydride, aromatic aldehydes, and ethyl cyanoacetate for the synthesis of 1*H*-pyrazolo[1, 2-*b*]phthalazine-5, 10-dione derivatives mediated by L-proline in excellent yields is reported.

Graphical Abstract:



KEYWORDS: multicomponent reactions; one-pot synthesis; phthalimide; phthalic anhydride; ethyl cyanoacetate; pyrazolo[1,2-*b*]phthalazine-5-dione; organocatalyst.

INTRODUCTION

After the discovery of multicomponent reactions (MCRs) in 1850 by Strecker,[1] the concept has grown substantial interest in organic chemistry because it provides essential products in a single step by the creation of several new bonds in one pot. In drug discovery as well as in 'green chemistry',[2] MCRs are the chosen strategies due to convenient synthesis of compounds in a cost and time-effective manner.[3, 4]

Heterocycles containing the pyrazole core are important targets in synthetic and in medicinal chemistry because this unit is a potential moiety in numerous biologically active compounds,[5–8] among them viagra **1** & celecoxib **2** are notable. Similarly, phthalazine containing heterocyclic moiety are of great interest because they show enough pharmacological and biological activities.[9–12] As an evidence, pyrazolo [1, 2-b] phthalazine-dione derivatives **4** have been reported as anti-inflammatory, analgesic, anti-hypoxic and antipyretic agents.[9,10] Moreover, phthalazine derivatives has reported to possess anticonvulsant, cardiotonic, vasorelaxant, antimicrobial, antifungal, anticancer and anti-inflammatory activities[13, 14] (Figure 1).

Despite their wide utility range, few methods have been reported for the synthesis of pyrazolo [1, 2-b] phthalazine-dione.[15] Apparently, some methods suffer from drawbacks such as relative toxic catalyst, sophisticated reaction arrangements, limited examples etc. Besides the available methods, the development of new synthetic methods for the efficient construction of heterocycles containing a phthalazine moiety is therefore an interesting challenge. Recently, multicomponent reactions of alkyl cyanoacetate, an

aldehyde and nucleophilic compounds have attracted a lot to the chemists because the formation of different condensation products can be expected depending upon the specific conditions, catalysts and structure of the building blocks.[16–20] To the best of our knowledge, few multicomponent reactions were conducted by organocatalyst,[21] especially with L-proline. Our current attempts in screening organocatalyst to multicomponent reaction envisaged us herein to report the synthesis of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-diones derivatives using L-proline to condense phthalimide / phthalic anhydride, hydrazine monohydrate, benzaldehyde and ethyl cyanoacetate.

RESULT AND DISCUSSION

As an effort in selecting suitable organocatalyst to multicomponent reaction, initially we attempted a four-component reaction of phthalimide or phthalic anhydride **5**, hydrazine mono-hydrate **6**, ethyl cyanoacetate **7** and bezaldehyde **8** by picolinic acid at the refluxing temperature of ethanol (Scheme 1). As we know, picolinic acid by its dual nature can exert organocatalytic activity to some organic transformation and therefore we were inspired to exploit it in the present reaction. But the use of 2- and 3- picolinic acid over the reacting components at different reaction conditions did not bring about any noticeable changes in TLC. From our earlier experiences,[22] later we wished to use L-cystein to the same reaction and monitored the reaction at different temperatures, solvents and catalyst loadings (Table 1). Interestingly for a few examples, L-cystein is somewhat working but the percentage of conversion is not satisfactory. Therefore, we have undertaken rigorous precautions to make the reaction fruitful by the alteration of reaction temperatures, solvents and variation of catalyst loadings. But all the efforts went in vain

to achieve the target product to a desired level. L-proline is now considered as the simplest enzymatic catalyst and are exploiting as a versatile organocatalyst in many enantioselective transformations.[23] Rigid ring structure,[24] easy availability, non toxic nature and enough durability in air make this tiny molecule significant in synthesizing different molecules of biologically interest.

Considering the modern 'paradigm shift' towards green synthesis, multicomponent reactions by organocatalysis are heartily welcomed. So, our third attempt is to use L-proline to the same four component condensation reaction. At the beginning, the reaction proceeded at a slower rate and incomplete conversion (~ 50 %) was observed even after 48 hrs reflux. Then we thought to use LiCl to the same reaction mixture aiming at to augment the electrophilicity of aldehyde functionality (Scheme 1) to achieve the maximum target. Fortunately, our idea turned into ~~got~~ reality and we have achieved maximum benefits by the addition of LiCl.

Therefore to set the optimistic conditions, reaction of phthalimide or phthalic anhydride (for **9f-9i**) with benzaldehyde, ethyl cyanoacetate and hydrazine mono-hydrate was performed at different temperatures to various solvents (CH_3CN, EtOH and H_2O) without and ~~&~~ with different amount of catalyst (5, 10, 15, 20 mol %, Table 1). Importantly, at room temperature without and with catalyst reaction does not proceed at all. But at 35 ^{0}C with 5 mol % catalyst loading, reaction proceeded at a very slower rate and incomplete conversion (10 ~ 25 %) was observed even after 48 hrs heating over the mentioned solvents. Maximum conversion (~50 %) was noticed at 80 ^{0}C in ethanol ~~with~~

by the single use of L- proline (10 mol %). Increment of the amount of catalyst from 15 to 20 mol% failed to afford significant improvement of both the yields and the reaction time. To our delight improved conversion (~ 93 %) was obtained whenever the solvent system was altered from ethanol to dual solvent system (ethanol / water; 1:1) accompanying LiCl (5 mol %) as a co-catalyst.

By this simple technique, reaction time was ~~has~~ surprisingly dropped down to 12 hr with full conversion (Table 2) of the reactants. To eliminate the ambiguity, LiCl (without L-proline) was employed to the same reaction but we did not discover any significant changes in TLC so, LiCl in this reaction is purely acting as a co-catalyst. Moreover, we also noticed using of excess L-proline (> 10 mol %) did not bring any additional benefits; on the contrary, it created difficulties to isolate the pure products.

To compare the yields and versatility of the present work, the same reaction was performed according to a recently published work.[15] Interestingly, a good compatibility was observed in the results and in some cases better efficacy was discovered. Later, we wished to make the four-component reaction general and therefore aldehydes with various groups were reacted. Interestingly, phthalimide and aldehydes with electron withdrawing groups were providing better yields and required shorter reaction time to completion. Noticeable electronic and structural effects were observed for the substrates **13-19** and in fact, no condensations were occurred at all. The failure may come from the negative charge accumulation onto the aldehydic carbon which deters nucleophilic attack, or the strong hydrogen bond formation possibility between the catalyst and the aldehyde

molecules may make the nucleophilic attack difficult. Reaction mechanism by L- proline is thought to be proceeded by the same fashion as depicted in the literature [25] (Scheme 2).

But in our case, L-Proline due to its -NH functionality forms imine intermediate **2** with the phthalimide **1** and later it undergoes a nucleophilic attack by the hydrazine and forms an imino hydrazine **3**. This imino hydrazine 3 with the expulsion of $-XH_2$ and catalyst L-proline forms phthalhydrazide **4** that is also vulnerable to attack by the activated enone **7** formed during Knoevenagel condensation. But before that, phthalhydrazide **4** may form imine **5** with L-proline and continues the initial condensation by the tandem fashion and leads to the final product.

As soon as the reaction complete, the resulting products float over the solvent mixture and by filtration enough pure products were isolated in excellent yields. By this technique we have synthesized twelve different 1H-pyrazolo [1, 2-b] phthalazine-5, 10-dione compounds. Some of the products are known in the literatures, so their melting points were compared with the literature values.[15, 25]

CONCLUSION

In summary, we have developed a one-pot four-component reaction for the synthesis of pyrazolo [1, 2-b] phthalazine-5, 10-diones derivatives from some available substituted aldehydes. The novelty of this method has proved by the first time uses of L-proline as

organocatalyst to the present multicomponent reaction. As a whole, it is concise, highly efficient, high yielding, friendly to the environment and inexpensive.

EXPERIMENTAL

General Procedure For The Preparation Of Phthalazine Derivatives (9)

A mixture of phthalimide / phthalic anhydride (147 mg), hydrazine hydrate (50 mg), L-proline (11 mg, 10 mol %) and LiCl (2 mg, 5 mol %) in ethanol: water (4 mL) was stirred at 80 ^{0}C for 4h with an efficient $CaCl_2$ guard tube over the reaction vessel. Then aromatic aldehyde, ethyl cyanoacetate (113 mg) were added sequentially to the mixture and it was again heated (80 ^{0}C) till completion of the reaction (monitored by TLC). After completion, the reaction mixture was allowed to cool to room temperature. A pale yellow colored product was appeared over the solvent mixture and it was separated by filtration. Finally, the product was washed with ethanol and for a few cases, recrystallization done by MeOH and specific rotations were measured for a few pure products (**9a, 9f, 9i** & **9j)**.

Spectral Data For Selected Compounds

(9a). Ethyl-3-amino-1-(4-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate : Pale yellow powder (90 %); mp. 242-244 ^{0}C; $[\alpha]_D^{25}$ = -0.71 (c=0.14, pyridine). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (3H, brs, -CH_3), 4.06-4.04 (2H, m, -OCH_2), 6.32 (1H, s, -CH), 7.61 (2H, d, J = 8 Hz, H-Ar), 7.87-7.89 (2H, m, H-Ar), 8.18 (2H, d, J = 8 Hz, H-Ar), 8.20-8.23(1H, m, H-Ar), 8.35-8.36 (1H, m, H-Ar) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.1, 59.8, 63.2, 123.6, 127.7, 127.9, 128.5, 128.7, 133.9,

135, 145.7, 147.7, 154.1, 157.2 ppm. HRMS calcd for $C_{20}H_{16}N_4O_6$: 408.3642, found: 408.3640.

(9f). Ethyl-3-amino-1-(4-chlorophenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (89 %); mp. 275-277 ^{0}C; $[\alpha]_D^{25}$ = -2.40 (c = 0.12, pyridine). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (3H, brs, -CH_3), 4.08 (2H, q, J = 7 Hz, -OCH_2), 6.26 (1H, s, CH), 7.30 (2H, t, J = 8 Hz, H-Ar), 7.40 (2H, d, J = 8 Hz, H-Ar), 7.86-7.90 (2H, m, H-Ar), 8.27-8.30 (1H, m, H-Ar), 8.35-8.37 (1H, m, H-Ar) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.2, 59.7, 63.4, 127.7, 127.7, 128.5, 128.6, 129, 129.1, 133.6, 134.07, 134.7, 137.1, 153.7, 157.2 ppm. HRMS calcd for $C_{20}H_{16}ClN_3O_4$: 397.8176, found: 397.8174.

(9i). Ethyl-3-amino-1-(3-methoxyphenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (87 %); mp. 256-258 ^{0}C; $[\alpha]_D^{25}$ = -1.89 (c = 0.18, pyridine). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (3H, t, J = 7 Hz, -CH_3), 3.80 (3H, s, -OMe), 4.09 (2H, q, J = 7 Hz, -OCH_2), 6.26 (1H, s, -CH), 6.83 (1H, dd, J = 2, 8, Hz, H-Ar), 6.98 (1H, t, J = 1.8 Hz, H-Ar), 7.05 (1H, d, J = 8 Hz, H-Ar), 7.26 (1H, q, J = 8 Hz, H-Ar), 7.84-7.89 (2H, m, H-Ar), 8.27-8.30 (1H, m, H-Ar), 8.34-8.37 (1H, m, H-Ar) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.2, 59.6, 63.9, 82.9, 113.4, 113.5, 120, 127.6, 127.7, 128.6, 129.3, 129.3,

133.4, 134.6, 140.3, 134.7, 137.1, 153.8, 157.2, 159.5 ppm. HRMS calcd for $C_{21}H_{19}N_3O_5$, 393.3960, Found: 393.3959.

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Table 1: Effects of catalysts, solvents & reaction temperature.[a]

Entry	Catalyst	mol %	Solvent	Temperature (^oC)	Time (hour)	yield (%)[b]
I	Without catalyst	-	CH_3CN, EtOH, H_2O	RT, Reflux (80)	> 48	No
II	2-or 3-picolinic acid	5, 10, 15, 20	CH_3CN, EtOH, H_2O	RT, Reflux (80)	> 48	No
III	L-cystein	5, 10, 15,20	CH_3CN, EtOH, H_2O	RT, Reflux (80)	> 48	No
IV	LiCl	10	CH_3CN, EtOH, H_2O	RT	> 48	No
V	LiCl	5~20	EtOH	40, 55, 60, Reflux (80)	> 48	30 ~ 32
VI	L-proline	5, 10	EtOH, H_2O	RT	> 48	No
VII	L-proline	5	CH_3CN, EtOH	35	> 48	10 ~ 25
VIII	L-proline	10	EtOH	Reflux (80)	20~24	~50
IX	L-proline + LiCl	10 + (~5)	EtOH	Reflux (80)	18~24	75
X	L-proline + LiCl	10 + (~5)	EtOH : H_2O (1:1)	Reflux (80)	10~12	91
XI	L-proline + LiCl	15 + (~5)	EtOH : H_2O (1:1)	Reflux (80)	10~12	89
XII	L-proline + LiCl	20 + (~5)	EtOH : H_2O (1:1)	Reflux (80)	10~12	88

[a]Reaction condition: aromatic aldehyde (1.0 mmol), phthalimide (1.0 mmol), hydrazine hydrate (1.2 mmol), ethyl cyanoacetate (1.0 mmol) and catalyst in solvent.

[b] Isolated yields.

Table 2: Synthesis of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-diones derivatives.[a]

Entry	Substituent on Aldehyde	Product	Time (hour)	Yield (%)[b]	M. p ^{0}C
1	4-$O_2NC_6H_4$-	9a	10~12	90	242-244
2	2-$O_2NC_6H_4$-	9b	10~12	87	238-241
3	3-$O_2NC_6H_4$-	9c	10~12	85	236-238
4	C_6H_5-	9d	10~12	88	245-247
5	$C_{10}H_7$-	9e	10~12	87	136-138
6	4-ClC_6H_4-	9f	10~12	89	275-277
7	2-ClC_6H_4-	9g	10~12	88	238-240
8	4-$CH_3OC_6H_4$-	9h	10~12	90	262-264
9	3-$CH_3OC_6H_4$-	9i	10~12	87	256-258
10	3-BrC_6H_4-	9j	10~12	88	199-200
11	4- $CH_3C_6H_4$-	9k	10~12	89	205-207
12	$C_7H_5O_2$-	9l	10~12	87	190-192
13	4-HOC_6H_4-	9m	> 48	No	
14	$C_6H_3C_2H_2(NH)$-	9n	> 48	No	
15	2,4-$(OH)_2C_6H_3$-	9o	> 48	No	
16	2-OH, 5-BrC_6H_3-	9p	> 48	No	
17	4-$(CH_3)_2NC_6H_4$-	9q	> 48	No	
18	2-HOC_6H_4-	9r	> 48	No	
19	C_4H_3O-	9s	> 48	No	

[a]Reaction condition: aromatic aldehyde (1.0 mmol), phthalimide (for coumpounds **9f**-**9i** phthalic anhydride was used) (1.0 mmol), hydrazine hydrate (1.2 mmol), ethyl cyanoacetae (1.0 mmol), L-proline (0.1 mmol) and LiCl (0.002 mmol) in ethanol : water (1:1).

[b]Isolated yield.

Scheme 1: Synthesis of 1*H*-pyrazolo [1, 2-*b*] phthalazine-5, 10-diones derivatives

Scheme 2: Tentative mechanistic path way for the formation of substituted phthalazine derivatives