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One-Pot Synthesis of Substituted Phthalazine-5,10-dione Derivatives in the Presence of Triflate Catalyst

Kadir TURHAN[1*]

ABSTRACT: In this study, substituted 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones which are considered that may possess biological activity have been obtained via one-pot multi-component cyclocondensation reaction of phthalhydrazide, aromatic aldehydes and malononitrile catalyzed in the presence of $Cu(OTf)_2$ in very good yields and short times. The structures of all these synthesized compounds (4a-f) have been determined and characterized by infrared, nuclear magnetic resonance, mass spectral data, and elemental analysis.

Keywords: Phthalazinedione, triflate, one-pot, multicomponent, green chemistry

[1] Kadir TURHAN (**Orcid ID:** 0000-0002-7718-1618), Yıldız Teknik Üniversitesi, Fen Edebiyat Fakültesi, Kimya, İstanbul, Türkiye

*Sorumlu yazar/Corresponding Author: Kadir TURHAN, kturhan@yildiz.edu.tr

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INTRODUCTION

Nowadays, green chemistry is attracting great attention due to the global population's ability to overcome environmental pollution problems. Green chemistry, also called sustainable chemistry, is a process that reduces or eliminates the use and production of hazardous substances. From this point of view, one-pot harmful solvent-free reactions are considered as an ideal method for green synthesis (Wender et al., 1997).

Pyrazolo[1,2-*b*]phthalazinediones are an important class of compounds that demonstrate biological activities such as analgesic, cytotoxic, cardiotonic, vasorelaxant, anti-allergic, antimicrobial, antifungal, anti-hypoxic, anticonvulsant, antipyretic, anti-inflammatory and antiviral (Wei et al., 2006; Xia et al., 2007; Vera-DiVaio et al., 2009; Lv et al., 2010; Nabid et al., 2010; Zhang et al., 2010; Raghuvanshi and Singh, 2011; Kiasat and Davarpanah, 2013; Bashti et al., 2015). Because of these properties, it is important to develop non-complex methods to obtain substituted 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives.

In the synthesis of substituted 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives, there are only a few studies on the synthesis of one-pot three-component phthalhydrazine, aromatic aldehydes, and malononitrile together with acidic or basic catalysts. However, most of the processes mentioned have disadvantages such as low yields, long reaction times, application of toxic or unsafe catalysts, expensive methods or more difficult reaction conditions (Lv et al., 2010; Reddy and Jeong, 2013; Bashti et al., 2015; Dabholkar et al., 2017; Dabholkar et al., 2018).

Metal salts of trifluoromethanesulfonic acid (metal triflates) are a new type of Lewis acid and are powerful catalysts for several organic syntheses. Due to their high stability, water tolerance, and recoverability from water, they are frequently used in organic synthesis as a catalyst (Kobayashi et al., 2002). There are many publications on the synthesis of substituted 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives in the literature (Teimouri, 2006; Ghahremanzadeh et al., 2008; Torkiana et al., 2011; Shah et al., 2012; Shaterian and Mohammadnia, 2012; Song et al., 2012; Ghomi et al., 2014; Kefayati et al. 2014; Reddy et al., 2014; Vaghei et al., 2014; Vafaee et al.,2015; Kefayati et al. 2016; Roy et al., 2016; Sangani et al., 2016; Lamera et al., 2017; Piltan, 2017; Mohamadpour et al., 2018), but none of them are related to their synthesis in the presence of metal triflate catalyst. This article reports the synthesis of substituted 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives catalyzed by $Cu(OTf)_2$ catalyst by the one-pot multicomponent reaction starting from the corresponding phthalhydrazide with substituted benzaldehyde and malononitrile at 80 °C. This synthetic method is consistent with the green chemistry approach because it defines an environmentally friendly, efficient and economical reaction that occurs at low temperatures without any harmful solvents and catalysts (Figure 1).

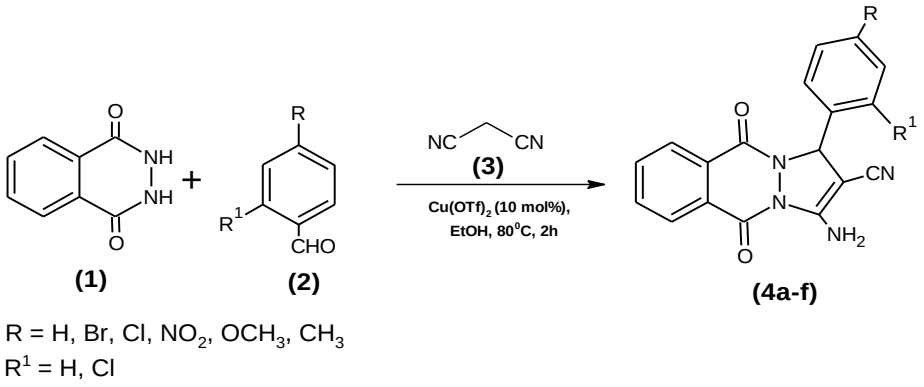

Figure 1. One-pot synthesis of substituted 1*H*-pyrazolo[1,2-*b*] phthalazine-5,10-diones

MATERIALS AND METHODS

Reagents purchased from Merck were as follows: ethanol, dichloromethane, chloroform, ethyl acetate, n-hexane, phthalhydrazide, benzaldehyde, p-bromobenzaldehyde, p-nitrobenzaldehyde, p-methoxybenzaldehyde, p-methylbenzaldehyde, 3,5-dichloro-benzaldehyde, malononitrile, copper(II) trifluoromethanesulfonic acid, silica gel 60 (0.063-0.200 mm), and sea sand. All reagents were available commercially and used without further purification in the reactions. TLC was carried out on aluminum sheets pre-coated with silica gel 60 F254 purchased from Merck, and the spots were visualized with UV light (254/366 nm) using a Camag UV lamp.

^{1}H NMR and ^{13}C NMR spectra were saved on "Bruker 500 MHz" spectrometers, in chloroform-*d* ($CDCl_3$) or DMSO using the tetramethylsilane (TMS) standard according to the solubility of the materials. FT-IR spectra were recorded on a "Philips PU 9714 ATR spectrophotometer", using the "Perkin-Elmer Spectrum One" program. Mass spectra (MS) were obtained with 70 eV "Hewlett Packard GC/MS 6890/5973". Melting points were obtained with a Gallenkamp Melting Point Apparatus in open capillaries with no correction.

General Procedure for the One-Pot Synthesis of 1*H*-pyrazolo[1,2-*b*] phthalazine-5,10-dione Derivatives (4a-f)

A mixture of phthalhydrazide (**1**) (1 mmol), substituted benzaldehyde (**2**) (1 mmol), malononitrile (**3**) (1 mmol), $Cu(OTf)_2$ (10 mol %) in ethanol (5 mL) was refluxed at 80^0C for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude product was filtered and then washed with water. The solid product was purified by recrystallization procedure in ethanol or column chromatography. All the products were characterized by spectroscopic data (FTIR, ^{1}H NMR, ^{13}C NMR, MS and EA) after the purification processes.

3-Amino-5,10-dioxo-1-phenyl-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (4a)

Yellow crystalline, mp. 272-74 ^{o}C. FTIR(ATR): υ= 3361, 3313, 3016, 2897, 2198, 1661, 1494, 1380, 792 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ= 6.13 (s, 1H), 7.33 (2H, d, *J*=7.08 Hz, Ar), 7.36 (1H, brd, *J*=7.52 Hz, Ar), 7.46 (2H, d, *J*=6.98 Hz, Ar), 7.97 (2H, brd, *J*=5.40 Hz, Ar), 8.08 (2H, s, NH_2), 8.10 (1H, brd, *J*=5.70 Hz, Ar), 8.27 (1H, brd, *J*=5.60 Hz, Ar) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ= 61.31, 116.03, 126.77, 127.29, 128.27, 128.52, 128.65, 133.73, 134.66, 150.83, 154.78, 156.82 ppm. GC-MS: m/z=316[M^{+}]. Anal. calcd. for

$C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71 Found: C, 68.49; H, 4.01; N, 17.65.

3-Amino-1-(4-bromophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*] phthalazine-2-carbonitrile (4b)

Light yellow crystalline, mp. 264-66 ^oC. FTIR (ATR): υ= 3375, 3306 3022, 2897, 2200, 1662, 1563, 1380, 1277, 846 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ=6.14 (s, 1H, CH), 7.46 (2H, d, *J*=8.35 Hz, Ar), 7.58 (2H, d, *J*=8.30 Hz, Ar), 7.98 (2H, dd, *J*=4.65; 4.30 Hz, Ar), 8.09 (1H, dd, *J*=5.40; 3.55 Hz, Ar), 8.14 (2H, s, NH_2), 8.27 (1H, dd, *J*=5.05; 3.90 Hz, Ar) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ= 62.73, 116.18, 122.79, 127.69, 128.64, 128.98, 134.66, 145.85, 147.36, 150.93, 153.78, 156.71 ppm. GC-MS: m/z= 395[M^+]. Anal. calcd. for $C_{18}H_{11}BrN_4O_2$: C, 54.70; H, 2.81; N, 14.18. Found: C, 54.98; H, 2.92; N, 14.27.

3-Amino-1-(4-nitrophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*] phthalazine-2-carbonitrile (4c)

Light yellow crystalline, mp. 266-68 ^oC, FTIR (ATR): υ= 3433, 3323 3075, 2927, 2198, 1680, 1657, 1516, 1380, 1277, 870 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ= 6.30 (s, 1H), 7.82 (2H, d, *J*=8.75 Hz, Ar), 7.99 (2H, dd, *J*=6.50; 2.45 Hz, Ar), 8.09 (1H, dd, *J*=6.55; 2.40 Hz, Ar), 8.20 (2H, s, NH_2), 8.23 (2H, d, *J*=8.80 Hz, Ar), 8.29 (1H, dd, *J*=6.65; 2.30 Hz, Ar) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ= 62.04, 115.78, 123.79, 127.29, 128.04, 128.98, 134.66, 145.85, 147.36, 150.93, 153.78, 156.71 ppm. GC-MS: m/z= 361[M^+]. Anal. calcd. for $C_{18}H_{11}N_5O_4$: C, 59.84; H, 3.07; N, 19.38. Found: C, 60.02; H, 3.16; N, 19.43.

3-Amino-1-(4-methoxyphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*] phthalazine-2-carbonitrile (4d)

Yellow crystalline, mp. 264-66 ^oC, FTIR (ATR): υ= 3367, 3264, 3010, 2890, 2188, 1680, 1655, 1489, 1378, 823, 779 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ= 3.76 (s, 3H, OCH_3), 6.10 (s, 1H, CH), 6.92 (2H, d, *J*=8.75 Hz, Ar), 7.39 (2H, d, *J*=8.73 Hz, Ar), 7.89 (2H, dd, *J*=5.93; 3.30 Hz, Ar), 7.97 (1H, dd, *J*=5.90; 3.30 Hz, Ar), 8.08 (2H, s, NH_2), 8.26 (1H, dd, *J*=5.91; 3.07 Hz, Ar) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ= 39.35, 61.43, 113.84, 125.13, 127.26, 128.47, 128.74, 132.58, 133.68, 134.65, 150.57, 153.59, 156.61 ppm. GC-MS: m/z= 346[M^+]. Anal. calcd. for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18. Found: C, 65.93; H, 4.09; N, 16.21.

3-Amino-1-(4-methylphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*] phthalazine-2-carbonitrile (4e)

Yellow crystalline, mp. 253-55 ^oC, FTIR (ATR): υ= 3357, 3259, 3034, 2903, 2195, 1679, 1651, 1470, 1378, 823, 734 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ= 2.30 (s, 3H, CH_3), 6.09 (s, 1H, CH), 7.17 (2H, d, *J*=8.02 Hz, Ar), 7.33 (2H, d, *J*=8.06 Hz, Ar), 7.97 (2H, dd, *J*=5.90; 3.30 Hz, Ar), 8.06 (2H, s, NH_2), 8.09 (1H, dd, *J*=5.80; 3.00 Hz, Ar), 8.26 (1H, dd, *J*=5.82; 3.30 Hz, Ar) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ= 20.90, 61.48, 116.03, 126.81, 127.26, 128.67, 129.04, 133.69, 134.64, 135.38, 150.56, 153.56, 156.60 ppm. GC-MS: m/z= 331[M^+]. Anal. calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 69.13; H, 4.23; N, 16.91.

3-Amino-1-(2,4-dichlorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*] phthalazine-2-carbonitrile (4f)

Pale yellow crystalline, mp. 258-60 ^oC, FTIR (ATR): υ= 3368, 3237, 3012, 2927, 2207, 1674, 1657, 1468, 1377, 1277, 840, 720 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): 6.45 (s, 1H, CH), 7.42 (1H, dd, *J*=8.42; 2.03 Hz, Ar), 7.67 (1H, d, *J*=2.11 Hz, Ar), 7.69 (1H, d, *J*=8.47 Hz, Ar), 7.99 (2H, dd, *J*=5.90; 3.20 Hz, Ar), 8.10 (1H, dd, *J*=5.90; 3.10 Hz, Ar), 8.17 (2H, s, NH_2), 8.29 (1H, dd, *J*=5.82; 3.30 Hz, Ar) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ= 59.74, 115.56,

126.71, 127.35, 128.05, 128.28, 128.84, 132.27, 133.60, 133.92, 134.76, 151.25, 153.61, 156.68 ppm. GC-MS: m/z= 386[M^+]. Anal. calcd. for $C_{18}H_{10}Cl_2N_4O_2$: C, 56.12; H, 2.62; Cl, 18.41; N, 14,54. Found: C, 56.15; H, 2.66; Cl, 18.42; N, 14,59.

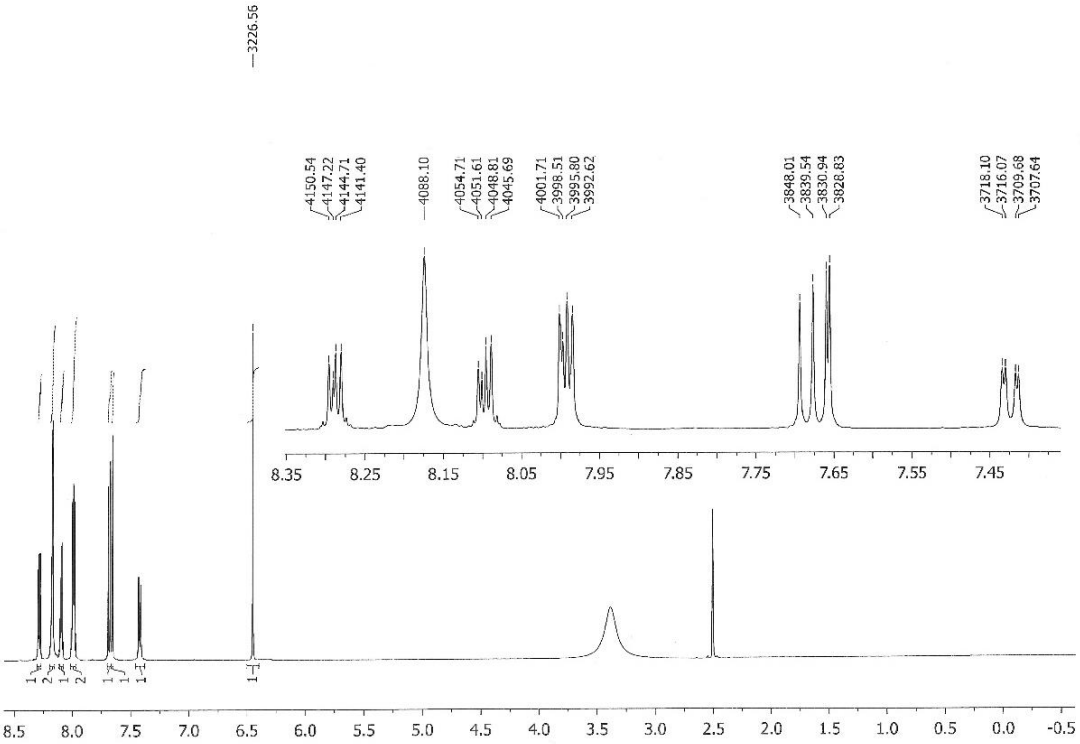

Figure 2. ^{1}H NMR spectrum of **4f** from synthesized compounds

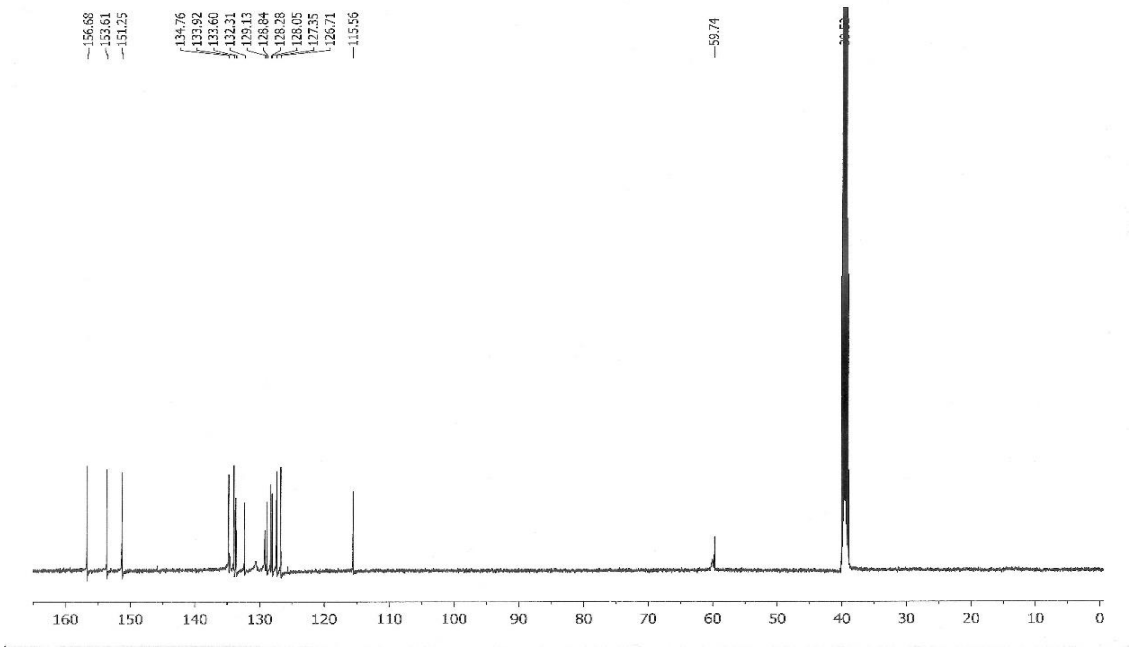

Figure 3. ^{13}C NMR spectrum of **4f** from synthesized compounds

RESULTS AND DISCUSSION

Metal triflates have been of great interest as catalysts over the past three decades due to their Lewis acid properties and effective functional group transformations catalyzed by these compounds. It has been well known that lanthanide triflates [$Ln(OTf)_3$], and their derivatives are Lewis acids which are stable. It can be used in green chemical methods due to its stability in water. Therefore metal triflates $M(OTf)_x$ are often used in a variety of organic reactions. Phthalazine derivatives are obtained in the presence of copper(II) triflate as recoverable acid catalysts under moderate reaction conditions by a simple, green and efficient process.

The catalytic effect of $Cu(OTf)_2$ was compared with some metal catalysts which were used widely for this reaction. For this purpose, the one-pot three-component reaction was carried out as a model reaction with phthalhydrazide, benzaldehyde and malononitrile in ethanol (synthesis of 3-amino-5,10-dioxo-1-phenyl-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile, **4a**). It was shown that $Cu(OTf)_2$ was best catalyst among them with lower catalyst amounts. The appropriate amount of $Cu(OTf)_2$ was found to be 10 mol %. All the results are given in Table 1.

Table 1. The reactions of phthalhydrazide, 1,3-cyclohexadione and benzaldehyde (4a); effect of catalysts.[a]

Entry	Catalyst	Used reactions	Amount of catalyst (mol%)	Time (h)	Yield (%)[b]
1	None	4a	---	24	38
2	$AlCl_3$	4a	100	24	47
3	$ZnCl_2$	4a	100	24	45
4	$FeCl_3$	4a	100	24	48
5	$Cu(OTf)_2$	4a	5	2	82
6	$Cu(OTf)_2$	4a	10	2	89
7	$Cu(OTf)_2$	4a	15	2	89
8	$Cu(OTf)_2$	4a	20	2	87

[a] All reactions were carried out under reflux in ethanol.
[b] Isolated yields.

A mechanism for the activity of $Cu(OTf)_2$ in the synthesis of 1*H*-pyrazolo[1,2-*b*] phthalazine-5,10-dione derivatives could be postulated as shown in Figure 4 (Reddy and Jeong, 2013; Eswararao et al., 2017).

The reaction possible take shape by Knoevenagel condensation between aldehyde (**2**) and malononitrile (**3**) on the acidic activity of $Cu(OTf)_2$ to form **5**. Then Michael type addition to 2,3-dihydrophthalazine-1,4-dione (**1**), followed by ring closure and tautomerization to form **4a-f**.

Under optimized conditions compounds 4a-f were synthesized with different aldehydes with high yields and short reaction time as shown in the Table 2. The structures of known compounds (**4a-f**) were in accordance with their spectral data (Ghorbani-Vaghei et al., 2014; Abdesheikhi and Karimi-Jaberi, 2015; Ghorbani-Vaghei et al., 2016; Kerayati et al., 2016; Mohamadpour et al., 2016; Wang et al., 2016; Arora and Rajput, 2017; Eswararao et al., 2017; Tayade and Dalal, 2017; Sabour et al., 2018; Shaikh et al., 2018).

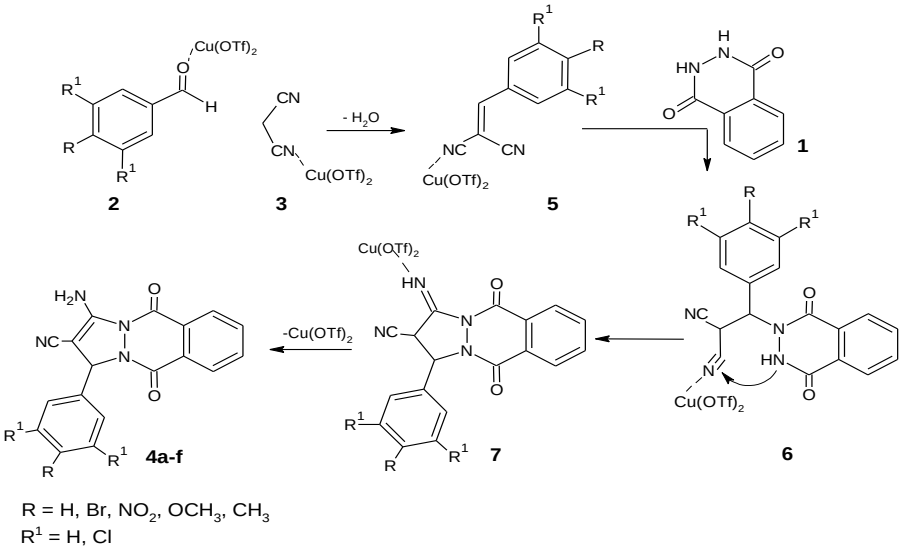

Figure 4. A schematic mechanism for the activity of $Cu(OTf)_2$ in the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives.

Table 2. Preparation of 1*H*-pyrazolo[1,2-*b*] phthalazine-5,10-dione derivatives[a].

Entry	R	R^1	Product	Time	Yield (%)[b]
1	H	H	4a	2 h	89
2	Br	H	4b	2 h	91
3	NO_2	H	4c	3 h	93
4	CH_3O	H	4d	2 h	89
5	H	Cl	4e	2 h	87
6	CH_3	H	4f	2 h	86

[a] All reactions were carried out in ethanol at 80^0C in the presence of $Cu(OTf)_2$ (10 mol%).
[b] Isolated yields

To investigate the catalyst activity, the catalyst was reused six times in the one-pot multi-component condensation of phthalhydrazide, benzaldehyde and malononitrile at 80 ^{0}C. In this procedure, after the completion of each reaction, $Cu(OTf)_2$ was washed with hot water and filtered. The recovered $Cu(OTf)_2$ was dried and reused. As shown in Figure 5, very low losses were observed in the catalytic activity of $Cu(OTf)_2$.

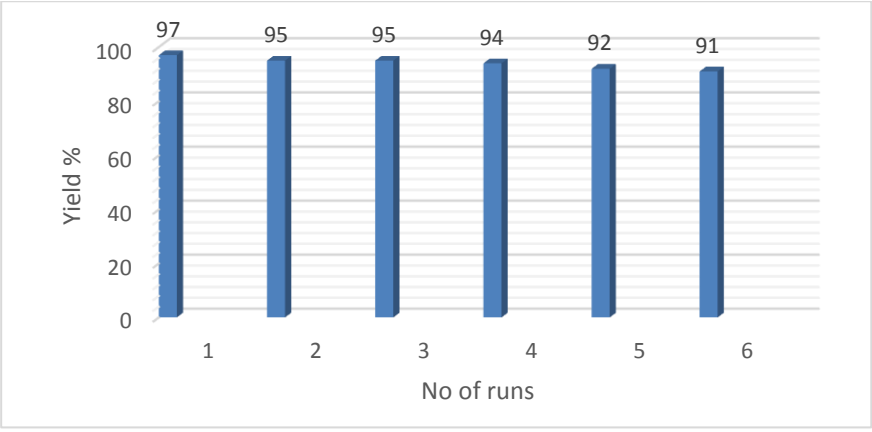

Figure 5. Reusability of the catalyst in the reaction.

CONCLUSION

In the study, it has been found that the synthesis of bioactive phthalazine derivatives with metal triflate takes place in excellent yields and short times, and metal triflates have an environmentally beneficial, economically applicable and reusable catalytic capability. Using this method offers many advantages under solvent-free conditions, which are considered to be relatively eco-friendly, such as very good yield, low catalyst amount, less reaction time, easier handling and multi-component reaction. Therefore, this article is thought to lead to future studies.

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