COMBINING A CLICK–MULTICOMPONENT REACTION: ONE-POT SYNTHESIS OF 1,2,3-TRIAZOL-4-YLMETHYL 3-AMINO-5,10-DIHYDRO-5,10-DIOXO-1H-PYRAZOLO[1,2-b]PHTHALAZINE-2-CARBOXYLATE DERIVATIVES

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GRAPHICAL ABSTRACT

Abstract (1,2,3-Triazol-4-yl)methyl-3-amino-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate derivatives were synthesized by a four-component, one-pot condensation reaction of benzaldehyde derivatives, an active methylene compound (prop-2-ynyl-2-cyanoacetate), azides, and phthalhydrazide in the presence of Cu(OAc)2/sodium ascorbate as catalysts and 1-methyl-1H-imidazolium trifluoroacetate ([Hmim]TFA) as an ionic liquid medium in good to excellent yields.

Keywords 1,3-Dipolar cycloaddition; multicomponent reaction; pyrazolo[1,2-b]phthalazine-2-carboxylate derivatives; 1,2,3-triazoles

INTRODUCTION

Multicomponent reactions (MCRs) have emerged as an efficient synthetic strategy over conventional linear-type synthesis because of their flexible, atom-efficient nature and ability to create several new bonds in a one-pot reaction. Therefore, they can achieve combinatorial synthesis of heterocyclic compounds.[1]

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Nitrogen-containing heterocyclic compounds play an important role in biological systems. Among them, phthalazine derivatives are important targets in synthetic and medicinal chemistry, because of their biological properties. Phthalazine derivatives that have two bridgehead nitrogen atoms possess cytotoxic, antimicrobial, anticonvulsant, antifungal, anticancer, and anti-inflammatory activities.

Recent protocols directed toward designing structural motifs containing the phthalazine ring fragment usually employ multicomponent condensation of aldehydes and active methylene compounds (malononitrile, ethyl cyanoacetate, and dinedone) with 2,3-dihydro-1,4-phthalazinedione, also known as phthalhydrazides.

"Click chemistry," introduced by Kolb et al., has become a popular method in chemistry because of its efficient approach for the synthesis of valuable compounds. One of the most reliable "click reactions" is Huisgen’s thermal 1,3-dipolar cycloaddition between alkynes and azides leading to 1,2,3-triazoles, which are reported to have several biological activities, such as anti-HIV, antiallergic, antifungal, and antimicrobial.

As a part of our continued interest in the development of methods for the synthesis of heterocyclic compounds coupled with our experience in the combination of multicomponent reactions and click chemistry, we report here a very simple and highly efficient method for the synthesis of 1,2,3-triazolo-4-ylmethyl-3-amino-5,10-dihydro-5,10-dioxo-1H-pyrazolo[1,2,b]phthalazine-2-carboxylates through a one-pot, four-component reaction. The structures of target molecules 5a–5p were constructed by a new four-component reaction of benzaldehyde derivatives 1a–1n, azides 2a–2e, an active methylene compound (prop-2-ynyl-2-cyanoacetate) (3), and phthalhydrazide (4) in the presence of Cu(OAc)₂ with sodium ascorbate as catalyst and 1-methyl-1H-imidazolium trifluoroacetate as an ionic liquid medium (Scheme 1).

![Scheme 1. One-pot, four-component reaction.](image-url)
RESULTS AND DISCUSSION

In our initial research, we studied the treatment of 4-chlorobenzaldehyde (1a) with 3-nitrophenyl azide (2a), prop-2-ynyl 2-cyanoacetate (3), and phthalhydrazide (4) under different conditions (Table 1). By using Cu(OAc)$_2$/sodium ascorbate as the catalyst, the reaction was tested employing various solvents such as CH$_3$CN, CH$_2$Cl$_2$, water, and ethanol. It is worth mentioning that in the absence of catalyst as a Brønsted acid under reflux conditions the target compound was not formed at all (Table 1, entries 1–3). In the presence of $p$-TsOH as a Brønsted acid in water or ethanol as solvent the reaction was very slow and the product was obtained in poor yield (Table 1, entries 4 and 5). After several attempts, it was found that by changing the solvent to [Hmim]TFA as an ionic liquid (IL) at 100°C, the desired product 5a was isolated in 81% yield (Table 1, entry 6). Using a different IL medium

Table 1. Optimization of reaction conditions

| Entry | Catalyst | Solvent (temperature) | Yield (%) |
|-------|----------|-----------------------|-----------|
| 1     | Cu(OAc)$_2$/NaAsc | CH$_2$Cl$_2$ (Reflux) | Trace     |
| 2     | Cu(OAc)$_2$/NaAsc | CH$_3$CN (reflux) | Trace     |
| 3     | Cu(OAc)$_2$/NaAsc | H$_2$O (reflux) | Trace     |
| 4$^b$ | $p$-TsOH·Cu(OAc)$_2$/NaAsc | H$_2$O (reflux) | 23        |
| 5$^b$ | Cu(OAc)$_2$/NaAsc/$p$-TsOH | EtOH (reflux) | 53        |
| 6$^c$ | Cu(OAc)$_2$/NaAsc | [Hmim]TFA (100°C) | 81        |
| 7$^c$ | Cu(OAc)$_2$/NaAsc | [Hmim]HSO$_4$ (100°C) | 67        |
| 8$^d$ | CuI | [Hmim]TFA (100°C) | 34        |
| 9$^e$ | CuSO$_4$/NaAsc | [Hmim]TFA (100°C) | 56        |
| 10$^e$ | CuCl$_2$/NaAsc | [Hmim]TFA (100°C) | 48        |
| 11$^e$ | Cu(OAc)$_2$/NaAsc | [Hmim]TFA (100°C) | 51        |
| 12$^e$ | Cu(OAc)$_2$/NaAsc | [Hmim]TFA (60°C) | Trace     |

$^a$Reaction conditions: 4-chlorobenzaldehyde 1a (0.14 g, 1 mmol), 1-azido-3-nitrobenzene 2a (0.16 g, 1 mmol), prop-2-ynyl 2-cyanoacetate 3 (0.14 g, 1.2 mmol), phthalhydrazide 4 (0.16 g, 1 mmol), Cu(OAc)$_2$ (0.02 g, 10 mol%), sodium ascorbate (0.04 g, 20 mol%), solvent (10 mL), 4 h.

$^b$Cu(OAc)$_2$ (0.02 g, 10 mol%), sodium ascorbate (0.04 g, 20 mol%), and $p$-TSA (0.34 g, 20 mol%).

$^c$Cu(OAc)$_2$ (0.02 g, 10 mol%), sodium ascorbate (0.04 g, 20 mol%), and [Hmim]TFA (10 mol%).

$^d$CuI (0.019 g, 10 mol%) and [Hmim]TFA (10 mol%).

$^e$CuSO$_4$ (0.016 g, 10 mol%), sodium ascorbate (0.04 g, 20 mol%), and [Hmim]TFA (10 mol%).

$^f$CuCl$_2$ (0.013 g, 10 mol%), sodium ascorbate (0.04 g, 20 mol%), and [Hmim]TFA (10 mol%).

$^g$Cu(OAc)$_2$ (0.01 g, 5 mol%), sodium ascorbate (0.02 g, 10 mol%), and [Hmim]TFA (10 mol%).
([Hmim]HSO$_4$) did not give an improved yield (Table 1, entry 7). Additionally, different copper sources such as CuI, CuCl$_2$, and CuSO$_4$ were screened in the model reaction using IL catalyst and gave product in poor to moderate yields (Table 1, entries 8–10). It was found that when the amount of the Cu decreased from 10 to 5 mol%, the yields decreased from 81 to 51%, respectively (Table 1, entry 11). It is noteworthy that compound 5a was not produced at lower reaction temperature (60°C) (Table 1, entry 12) but compound 7a was isolated instead.

Apparently, 7a is an intermediate of this reaction and higher temperature was needed for completion of the reaction (Scheme 2). To check the correctness of this hypothesis, compound 7a was synthesized and treated with compound 4 in the presence of [Hmim]TFA at 100°C; after 5 h, the desired product 5a was obtained in 80% yield.

With this optimized procedure in hand, the scope of the four-component reaction was examined by using other aromatic aldehydes 1a–1n, azides 2a–2e, prop-2-ynyl 2-cyanoacetate (3), and phthalhydrazide (4) in the presence of catalytic amounts of Cu(OAc)$_2$ (10 mol%), sodium ascorbate (20 mol%) and [Hmim]TFA at 100°C for 5–6 h. The results are summarized in Table 2. As can be seen, this transformation is very general for a variety of benzaldehyde derivatives and azides. As shown in Table 2, it was found that this procedure works with a wide variety of substrates. Both electron-rich and electron-deficient groups on the aromatic aldehydes can be used with equal success and five different types of azides were used in this reaction.

Although the exact mechanism of this transformation is not completely clear, a possible pathway for this four-component reaction could be proposed in three steps. First, formation of intermediate 6 by Knoevenagel condensation was followed by the 1,3-dipolar cycloaddition reaction between 6 and azide 2, leading to triazole derivative 7 as an intermediate produced from the click reaction. Then, the subsequent Michael-type addition of phthalhydrazide (4) would give the intermediate 8, followed by cyclization to afford the corresponding product 5 (Scheme 2).

The structures of the products 5a–5p were characterized by their spectroscopic data. The $^1$H NMR spectra of these compounds in dimethylsulfoxide (DMSO-$_d_6$)
Table 2. One-pot, four-component synthesis of triazolyl-phthalazine-2-carboxylates 5a–p

|   |   |   |   |
|---|---|---|---|
| HORCH  | R_1_N_3  |  | Cu(OAc)_2 |
| OMe | N | N | Sodium Ascorbate |
| |  |  | [Hmisn]TFA, 100 °C |
| 1a-1n | 2a-2e | 3 | 4 |
| 5a (81%) | 5b (75%) | 5c (78%) | 5d (74%) |
| 5e (78%) | 5f (76%) | 5g (82%) | 5h (85%) |
| 5i (72%) | 5j (73%) | 5k (69%) | 5l (78%) |
| 5m (75%) | 5n (73%) | 5o (70%) | 5p (74%) |

consisted of a characteristic peak belonging to the triazole H-atom in the region of δ = 8.25–8.85 ppm. In addition, the distinguishing peak for H-C(1) of the 1H-pyrazolo[1,2,3b]phthalazine-2-carboxylate moiety was observed at δ = 6.05–
6.44 ppm. Another characteristic feature of the $^1$H NMR spectra was the appearance of an AB signal at $\delta = 5.08-5.61$ ppm, which arises from the (triazol-4-yl)CH$_2$ unit.

Additionally, we checked the recycling of the ionic liquid. In the preparation of 5a, the [Hmim]TFA was reused for five runs. Second and third reactions using recovered ionic liquid afforded similar yields to those obtained in the first run. In the fourth and fifth runs, the yields were decreased (the yields of the product 5a were 81%, 80%, 78%, 72%, and 64%, respectively).

**CONCLUSION**

In summary, we have developed a highly efficient method for the construction of 1,2,3-triazol-4-ylmethyl-3-amino-5,10-dihydro-5,10-dioxo-$^1$H-pyrazolo[1,2-b]phthalazine-2-carboxylate skeleton via a one-pot, four-component condensation of aromatic aldehydes, azides, prop-2-ynyl-2-cyanoacetate, and phthalhydrazide for furnishing a class of derivatives in good yield and excellent atomic economy.

**EXPERIMENTAL**

Chemicals were purchased from commercial suppliers and were used without purification. Melting points were measured on an Electrothermal 9100 apparatus and were not corrected. High-resolution electrospray ionization–mass spectrometry (HR-ESIMS) spectra were acquired on a Bruker MicroTOF ESI-MS system. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively, or a Varian Unity 400 spectrometer at 400 and 100.6 MHz, respectively. Infrared (IR) spectra were recorded on a Bomem MB-Series FT-IR spectrometer.

**General Procedure for the Synthesis of Prop-2-ynyl 2-Cyanoacetate (3)**

Cyanoacetic acid (851 mg, 10 mmol) and prop-2-yn-1-ol (561 mg, 10 mmol) were dissolved in dichloromethane (40 mL) and cooled to 0°C. A solution of $N,N'$-dicyclohexylcarbodiimide (2.1 g, 10 mmol) and 4-dimethylaminopyridine (117 mg, 1 mmol) in dichloromethane (20 mL) was added, and the reaction mixture was stirred for 2 h at 0°C. The solid dicyclohexylurea was filtered, and the filtrate was concentrated to give an oil that was purified by SiO$_2$ chromatography (3:1 hexane-ethyl acetate) to give 1.05 g of 3 as a colorless oil (85%). $^1$H NMR (399.939 MHz, CDCl$_3$): $\delta = 2.55$ (t, 1H, $J = 2.4$ Hz), 3.53 (s, 2H), 4.78 (d, $J = 2.4$ Hz). $^{13}$C NMR (100.575 MHz, CDCl$_3$): $\delta = 24.7, 54.1, 76.2, 76.4, 112.7, 162.5$.

**General One-Pot Procedure for MCR–Click Reaction to Produce 1,2,3-Triazol-4-ylmethyl 3-Amino-5,10-dihydro-5,10-dioxo-$^1$H-pyrazolo[1,2-b]phthalazine-2-carboxylate 5a–5p**

A mixture of benzaldehyde derivatives 1a–1n (1.0 mmol), aryl azide 2a–2e (1.0 mmol), prop-2-ynyl 2-cyanoacetate (3) (1.0 mmol), and phthalhydrazide (4)
(1.0 mmol) in the presence of Cu(OAc)₂ (0.02 g, 10 mol%), sodium ascorbate (0.04 g, 20 mol%), and [Hmim]TFA (0.5 g) were mixed thoroughly and then stirred for 4–5 h at 100 °C. After cooling, ammonium hydroxide (2 mL) and water (5 mL) were added and stirred for 30 min. Then the solid was filtered and washed with hot ethanol to give the pure products.

Synthesis of (1-(3-Nitrophenyl)-1H-1triazol-4-yl)methyl 3-Amino-1-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carboxylate (5a)

A mixture of 4-chlorobenzaldehyde (1a) (0.14 g, 1.0 mmol), 3-nitrophenylazide (2a) (0.16 g, 1.0 mmol), prop-2-ynyl 2-cyanoacetate (3) (0.12 g, 1.0 mmol), and phthalhydrazide (4) (0.16 g, 1.0 mmol) in the presence of Cu(OAc)₂ (0.02 g, 10 mol%), sodium ascorbate (0.04 g, 20 mol%), and [Hmim]TFA (0.5 g) were mixed thoroughly and then stirred for 4 h at 100 °C. After cooling, ammonium hydroxide (2 mL) and water (5 mL) were added and stirred for 30 min. Then the solid was filtered and washed with hot ethanol. Finally, the pure product 5a was obtained in 81% yield. Mp: 218–219 °C. IR (KBr) (νmax/cm⁻¹): 3463, 3303, 1697, 1672, 1650, 1536, 1391. ¹H NMR (300.13 MHz, DMSO-d₆): δ = 5.15 (d, 1H, J = 13.0 Hz, CH), 5.25 (d, 1H, J = 13.0 Hz, CH), 6.10 (s, 1H, CH), 7.19 (d, 2H, J = 8.1 Hz, HAr), 7.42 (d, 2H, J = 8.1 Hz, HAr), 7.88–8.39 (m, 9H, HAr,N H₂), 8.70 (s, 1H, HAr). ¹³C NMR (75.47 MHz, DMSO-d₆): δ = 56.1, 62.9, 81.1, 115.2, 123.2, 123.7, 126.6, 127.1, 127.7, 128.2, 129.2, 129.9, 132.1, 132.5, 134.1, 135.2, 137.5, 139.1, 149.0, 153.7, 157.4, 163.8. HR-MS (ESI) calcd. for C₂₇H₁₈ClN₇O₆ [M-H] 570.0934; found 570.0928.

Ionic liquid was recovered by washing the reaction mixture with CH₂Cl₂ and then evaporating it in vacuum. The recovered IL was washed with diethyl ether and can be reused for the same reactions.

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SUPPLEMENTARY MATERIAL

Experimental details and full characterization of compounds 5a–5p, 6a, and 7a, including ¹H and ¹³C spectra, can be accessed on the publisher’s website.

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