A Simple One-Pot Procedure for the Synthesis of 1,2,4-Triazolo[1,5-*a*]pyridines via Pseudo Five-Component Reactions Catalyzed by Molecular Iodine

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Abstract: In this paper we report the synthesis of the 1,2,4-triazolo[1,5-*a*]pyridine ring system. The reaction between benzylidenehydrazines, dialkyl acetylenedicarboxylates, benzaldehydes, and malononitrile proceeds in EtOH at reflux in the presence of molecular iodine as catalyst in good to excellent yields.

Key words: benzylidenehydrazine, dialkyl acetylenedicarboxylate, benzaldehyde, malononitrile, 1,2,4-triazolo[1,5-*a*]pyridine, catalyst, iodine, multicomponent reaction

The 1,2,4-triazole nucleus is an important structural motif present in a large number of functionalized molecules with a wide variety of uses, including applications in medicinal chemistry, materials science, and organocatalysis. As an example, 1,2,4-triazolo[1,5-*a*]pyridines[1] provided novel hinge binding motifs for the design of small-molecule ATP-competitive JAK2 inhibitors (Figure 1).

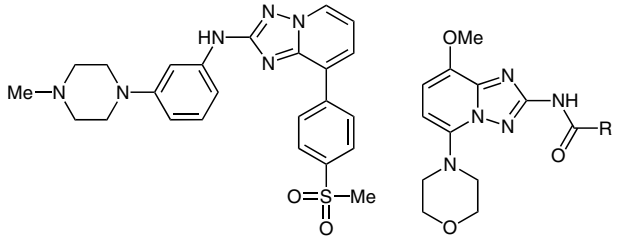
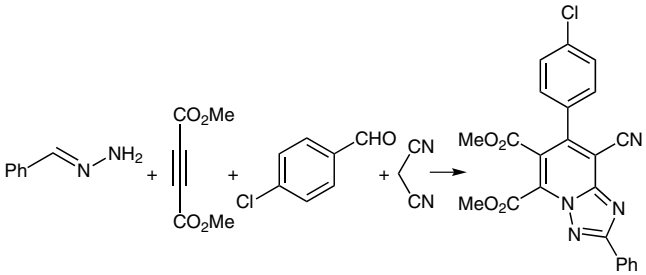


Figure 1 Biologically active compounds having a 1,2,4-triazolo[1,5-*a*]pyridine unit

This class of heterocycles is of considerable interest due to their use as antihypertensive, bronchodilatory, anti-inflammatory, analgesic, and positive inotropic agents.[2–4] The importance of this heterocyclic moiety has prompted the development of many practical synthetic routes to 1,2,4-triazole derivatives.[5] The majority of these routes rely on intramolecular condensation reactions of *N*-acylamidrazones obtained from hydrazines and carboxylic acid derivatives.[6] A number of literature[7] methods to prepare the 1,2,4-triazolo[1,5-*a*]pyridine core were evaluated and adapted to meet our design modifications. Although the existing synthetic methods have provided a wide variety of 1,2,4-triazolo[1,5-*a*]pyridine, these typically involve multistep reaction sequences. As part of our continuing efforts into the design of new routes for the preparation of biologically active compounds,[8] we report herein a single-step elaboration of 1,2,4-triazolo[1,5-*a*]pyridines using a conceptually distinct iodine-catalyzed oxidative coupling approach.

On the basis of the known ability of molecular iodine to activate imine bonds[9] and the recently developed catalytic construction of spiro nitrogen heterocycles,[10] we envisaged a direct synthesis of 1,2,4-triazolo[1,5-*a*]pyridines by reaction of hydrazones, dialkyl acetylenedicarboxylates, aldehydes, and malononitrile, leading initially to 1,4-dihydropyridines and then molecular-iodine-catalyzed C–N bond formation and synthesis of the 1,2,4-triazole nucleus. To explore this approach, we selected benzylidenehydrazine (**1a**), dimethyl acetylenedicarboxylate (**2a**), 4-chlorobenzaldehde (**3a**), and malononitrile for reaction development and screened molecular iodine in a range of solvents (Table 1). When **1a**, **2a**, **3a**, and malononitrile were reacted in the presence of 10 mol% molecular iodine in ethanol at reflux under air, dimethyl 7-(4-chlorophenyl)-8-cyano-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridine-5,6-dicarboxylate (**4a**)[11] was obtained in 75% yield (Table 1, entry 3).

Table 1 Synthesis of **4a** under Different Reaction Conditions



1a **2a** **3a** **4a**

Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	EtOH	I_2 (20)	5	74
2	EtOH	I_2 (15)	5	73
3	EtOH	I_2 (10)	5	75
4	MeCN	I_2 (20)	12	56
5	MeOH	I_2 (20)	12	61
6	EtOH	–	24	0

[a] Benzylidenehydrazine (1 mmol), dimethyl acetylenedicarboxylate (1 mmol), 4-chlorobenzaldehde (1 mmol), and malononitrile (1 mmol).

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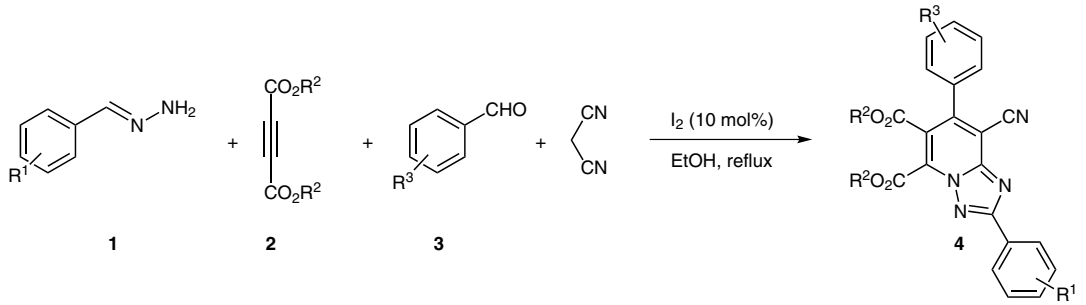
The reaction also proceeded in other solvents such as acetonitrile and methanol, albeit in lower yield (Table 1, entries 5 and 6). In another attempt, when the reaction was carried out in the absence of molecular iodine, no product was formed after 24 hours at 25 °C (Table 1, entry 6). Under the same reaction conditions, it was expectable to observe that similar high yields were obtained when the amount of molecular iodine was increased to 15 mol% or 20 mol% (74% and 73% yields, Table 1, entries 1 and 2).

With the optimum reaction conditions in hand, we next investigated the scope of the synthesis of 1,2,4-triazolo[1,5-*a*]pyridine (Table 2). Benzaldehydes with electron-withdrawing and electron-releasing groups gave the corresponding 1,2,4-triazolo[1,5-*a*]pyridines **4a**–**h** in good yield.

Table 2 Synthesis of 1,2,4-Triazolo[1,5-*a*]pyridine Derivatives



1 **2** **3** **4**

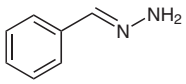
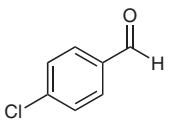
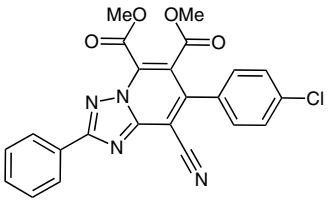
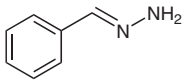
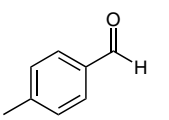
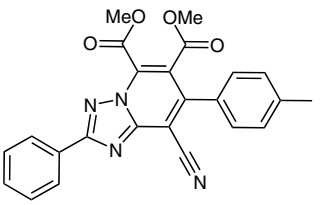
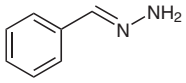
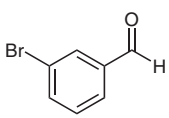
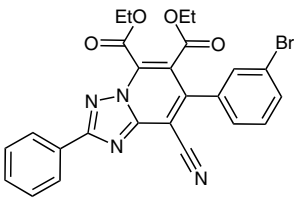
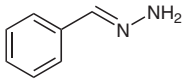
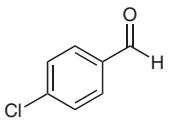
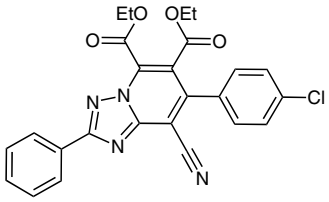
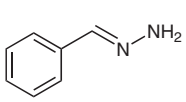
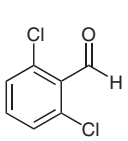
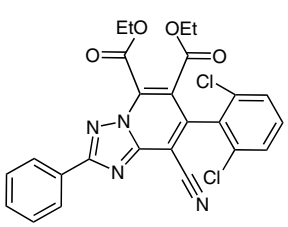
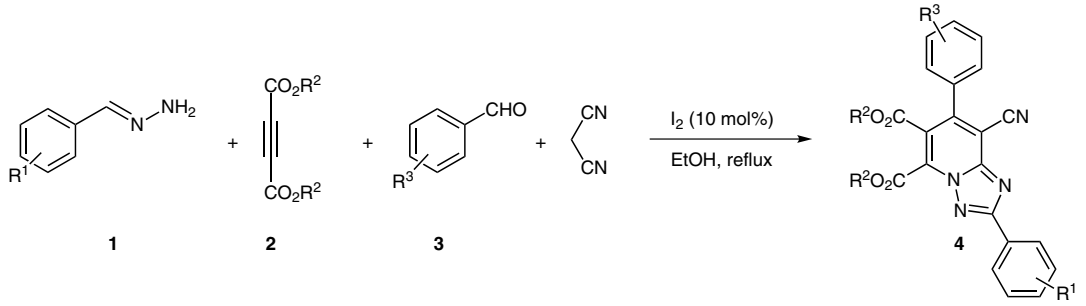
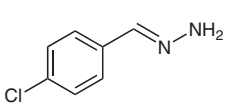
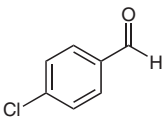
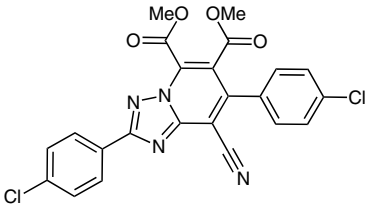
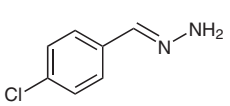
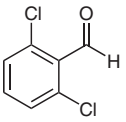
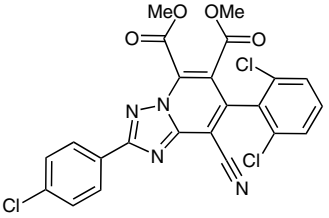
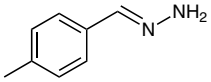
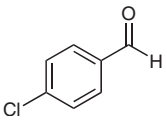
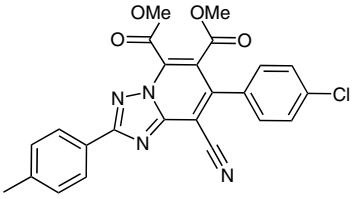
Entry	**1**	**2**	**3**	Product **4**	Yield (%)
4a					75
4b					70
4c					72
4d					76
4e					69

Table 2 Synthesis of 1,2,4-Triazolo[1,5-*a*]pyridine Derivatives (continued)

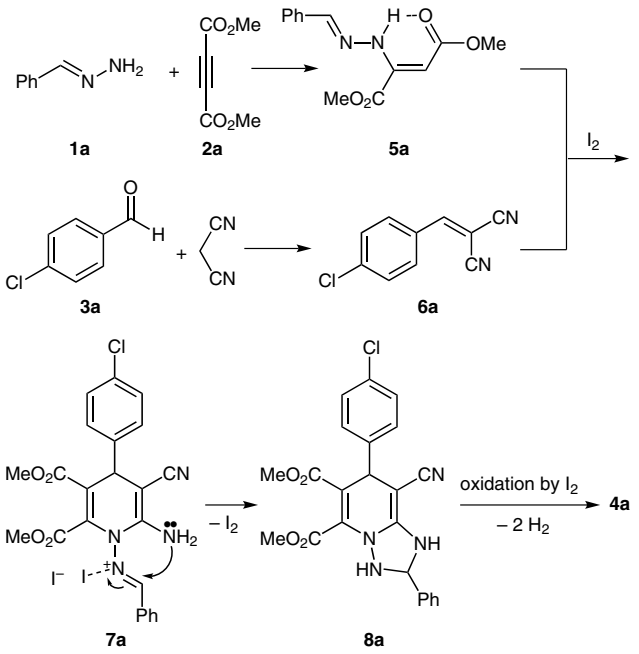


1 **2** **3** **4**

Entry	**1**	**2**	**3**	Product **4**	Yield (%)
4f					72
4g					68
4h					75

The structures of all products **4a**–**h** were elucidated from their mass, IR, and ^{1}H NMR and ^{13}C NMR spectra as described for **4a**. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 446, and the IR spectrum showed absorption bands due to the CN group at 2358 cm^{-1} and the CO_2Me groups at 1748 cm^{-1}. The ^{1}H NMR spectrum of **4a** showed two sharp singlets for 2 CH_3 groups (δ = 3.65 and 4.17 ppm) and the aromatic protons gave rise to multiplets in the region δ = 7.38–8.37 ppm. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances.

Although the detailed mechanism of the above reaction remains to be fully clarified, compound **4a** could be formed via attack of the benzylidenehydrazine on dimethyl acetylenedicarboxylate to yield enaminone **5a**, then reaction of enaminone **5a** with the product of Knoevenagel condensation **6a**, followed by loss of H_2O to give intermediate **7a**. In the next step molecular iodine could coordinate with the imine group with nucleophilic attack of the NH_2 group and finally oxidation of intermediate **8a** leading to the product. Evidence supporting this proposed mechanism came from the observation that when the intermediate **7a** was prepared in a separate exercise and subsequently reacted with molecular iodine under the same conditions, the expected product **4a** was obtained in a yield similar to that obtained in the one-pot reaction (Scheme 1).



Scheme 1 Probing the mechanism for the formation of title compounds

In conclusion we have developed a novel pseudo five-component synthesis of 1,2,4-triazolo[1,5-*a*]pyridines from benzylidenehydrazine, aromatic aldehydes, malononitrile, and acetylenic esters. The high yields, mild reaction conditions, ease of purification, and ready availability of the starting materials make this a convenient procedure for the synthesis of 1,2,4-triazolo[1,5-*a*]pyridines. This protocol not only provides a novel and effective methodology for the preparation of functionalized 1,2,4-triazolo[1,5-*a*]pyridines but also opens up the use of benzylidenehydrazine intermediates to design other similar multicomponent reactions. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

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(11) **Typical Procedure for the Preparation of Dimethyl 7-(4-Chlorophenyl)-8-cyano-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridine-5,6-dicarboxylate (4a)**

A solution of benzaldehyde (0.212 g, 2 mmol) and hydrazine hydrate (0.16 g, 1 mmol) was magnetically stirred in EtOH (5 mL) for 20 min. Then a solution of DMAD (0.142 g, 1 mmol) was added, and the mixture was stirred for 3 min. At this point, the condensation product of 4-chlorobenzaldehyde (0.140 g, 1 mmol) and malononitrile (**6a**, 0.066 g, 1 mmol) was added, and the reaction mixture was stirred for 3 h under reflux and progress was followed by TLC. After completion, the reaction mixture was cooled to r.t., I_2 (0.1 mmol) was added, and the mixture was stirred for a further 2 h. The progress of the reaction was again followed by TLC and, after completion, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (*n*-hexane–EtOAc, 5:1). All products gave satisfactory spectroscopic data in accordance with the assigned structures.

Representative Spectroscopic Data

Dimethyl 7-(4-Chlorophenyl)-8-cyano-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridine-5,6-dicarboxylate (4a)

White powder; yield: 0.26 g (59%); mp 263–265 °C. IR (KBr): 2358 (CN), 1748 (CO_2Me), 1538 and 1443 (Ar), 1251 (C–O of ester) cm^{-1}. ^1H NMR (500.13 MHz, $CDCl_3$): δ = 3.65 (3 H, s, OCH_3), 4.17 (3 H, s, OCH_3), 7.38 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar), 7.52–7.54 (5 H, m, 5 CH of Ar), 8.37 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar) ppm. ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 53.4 (OCH_3), 54.3 (OCH_3), 102.4 (C^8), 112.6 (C^5), 118.6 (CN), 128.3 (2 CH_{meta} of Ph), 128.8 (2 CH of Ar), 128.9 (C^6), 129.2 (2 CH of Ar), 129.7 (2 CH_{ortho} of Ph), 131.5 (CH_{para} of Ph), 132.8 (C_{ipso} of Ph), 135.3 (C–Cl), 136.5 (C_{ipso} of Ar), 147.6 (C^{8a}), 150.77 (C^7), 159.9 (C^2),163.6 (C=O), 167.8 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 446 (22) [M^+], 367 (35), 298 (31), 224 (22), 190 (36), 167 (22), 149 (57), 111 (28), 97 (46), 81 (57), 69 (100), 57 (65). Anal. Calcd (%) for $C_{23}H_{15}ClN_4O_4$ (446.85): C, 61.82; H, 3.38; N, 12.54. Found: C, 61.79; H, 3.39; N, 12.55.

Dimethyl 2,7-Bis(4-chlorophenyl)-8-cyano-[1,2,4]triazolo[1,5-*a*]pyridine-5,6-dicarboxylate (4f)

White powder; yield: 0.24 g (51%); mp 281–283 °C. IR (KBr): 2357 (CN), 1746 (CO_2Me), 1440 (Ar), 1259 (C–O of ester) cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 3.66 (3 H, OCH_3), 4.17 (3 H, OCH_3), 7.38 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar), 7.50 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar), 7.54 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar), 8.32 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 53.4 (OCH_3), 54.40 (OCH_3), 102.4 (C^8), 112.5 (C^5), 118.8 (CN),

127.3 (C^6), 129.1 (2 CH of Ar), 129.2 (2 CH of Ar), 129.5 (2 CH of Ar), 129.6 (2 CH of Ar), 132.6 (C_{ipso} of Ar), 135.2 (C–Cl), 136.7 (C_{ipso} of Ar), 137.7 (C–Cl) 147.7 (C^{8a}), 150.7 (C^7), 159.7 (C^2), 163.5 (C=O), 166.7 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 481 (31) [M^+], 480 (100) [$M^+ - 1$], 449 (22), 364 (51), 190 (22), 163 (22), 138 (72), 102 (30), 75 (53), 59 (33). Anal. Calcd (%) for $C_{23}H_{14}Cl_2N_4O_4$ (481.30): C, 57.40; H, 2.93; N, 11.64. Found: C, 57.42; H, 2.92; N, 11.65.

Dimethyl 7-(3-Bromophenyl)-8-cyano-2-*p*-tolyl-[1,2,4]triazolo[1,5-*a*]pyridine-5,6-dicarboxylate (4h)

White powder; yield: 0.25 g (55%); mp 287–289 °C. IR (KBr): 2359 (CN), 1742 (CO_2Me), 1441 (Ar), 1264 (C–O of ester) cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.45 (3 H, s, Me), 3.66 (3 H, OCH_3), 4.17 (3 H, OCH_3), 7.33 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar), 7.38 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar), 7.54 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar), 8.27 (2 H, d, $^3J_{HH}$ = 8.0 Hz, 2 CH of Ar) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 29.7 (Me), 53.3 (OCH_3), 54.3 (OCH_3), 100.2 (C^8), 112.7 (C^5), 118.3 (CN), 126.0 (C^6), 128.2 (2 CH of Ar), 129.2 (2 CH of Ar), 129.5 (2 CH of Ar), 129.6 (2 CH of Ar), 132.4 (C_{ipso} of Ar), 135.6 (C–Cl), 136.5 (C_{ipso} of Ar), 140.6 (C–Me), 142.0 (C^{8a}), 151.8 (C^7), 155.0 (C^2), 164.6 (C=O), 166.0 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 460 (53) [M^+], 422 (38), 391 (27), 364 (89), 199 (43), 163 (43), 138 (100), 111 (49), 75 (46), 59 (58) (32). Anal. Calcd (%) for $C_{24}H_{17}ClN_4O_4$ (460.87): C, 62.55; H, 3.72; N, 12.16. Found: C, 62.53; H, 3.73; N, 12.14.