



Synthesis of fully substituted pyrazolo[3,4-*b*]pyridine-5-carboxamide derivatives via a one-pot four-component reaction

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ABSTRACT

A one-pot four-component reaction of an aliphatic or aromatic amine, diketene, an aromatic aldehyde and 1,3-diphenyl-1*H*-pyrazol-5-amine in the presence of *p*-toluenesulfonic acid as a catalyst has been developed. In this reaction, a new class of fully substituted pyrazolo[3,4-*b*]pyridine-5-carboxamide derivatives is produced under mild reaction conditions and in good yields at ambient temperature.

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Multicomponent reactions (MCRs), are powerful synthetic tools which have changed the landscape of organic and medicinal chemistry because of environmental concerns, atom economy and their ability to generate large libraries of compounds in one synthetic step or two synthetic steps.^{1,2}

Pyrazolo[3,4-*b*]pyridines have received considerable attention and are of interest due to their wide variety of biological activities such as anxiolytic,^{3,4} inhibitors of xanthine oxidases,⁵ cholesterol formation-inhibiting compounds,⁶ treatment of Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and alcohol withdrawal symptoms, drug addiction and infertility.⁷ They have also been reported as potent and selective inhibitors of A1 adenosine receptors,⁸ phosphodiesterase 4 (PDE4) inhibitors in immune and inflammatory cells,⁹ glycogen synthase kinase-3 (GSK-3) inhibitors,¹⁰ kinase inhibitors of p38 α as anti-inflammatory drugs¹¹ as well as inhibitors of interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α) which are two multifunctional pro-inflammatory cytokines involved in the pathogenesis of cardiovascular and neurodegenerative diseases and cancer.¹²

Several methods are available for the synthesis of pyrazolo[3,4-*b*]pyridines. Some of the most efficient and commonly used methods are the copper- and palladium-promoted cyclization reactions of 2-chloro-3-cyanopyridine with hydrazines,¹³ the reaction of 5-aminopyrazoles with α,β -unsaturated ketones or their precursors, such as β -dimethyl-aminopropiophenones,¹⁴ condensation reactions of 5-aminopyrazoles, dimedone and aldehydes,¹⁵ Friedlän-

der-type condensation of 5-aminopyrazole-4-carbaldehydes with reactive α -methylene ketones,¹⁶ cycloaddition reactions of pyrazolyliimines with aromatic and aliphatic nitroalkenes under microwave irradiation¹⁷ and the reaction of dialdehydes with pyrazole and active methylene compounds under microwave irradiation.¹⁸ However, introduction of a simple protocol for the synthesis of a novel class of substituted pyrazolo[3,4-*b*]pyridine derivatives is important.

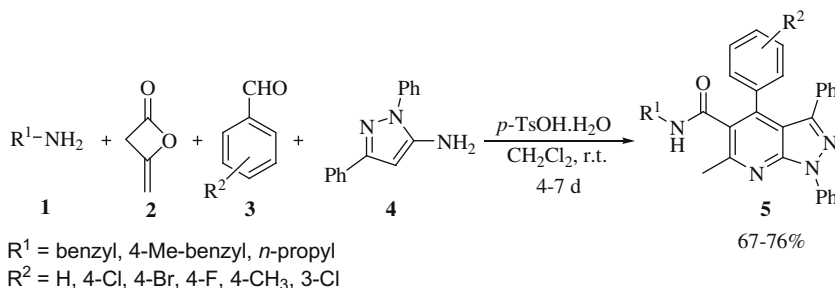
Keeping in mind the biological and pharmacological importance of pyrazolo[3,4-*b*]pyridines and in continuation of our interest in MCRs,^{19–23} we describe here the synthesis of novel substituted pyrazolo[3,4-*b*]pyridine-5-carboxamides **5**. This one-pot process involves a four-component condensation reaction of an aliphatic or aromatic amine **1**, diketene **2**, an aromatic aldehyde **3** and 1,3-diphenyl-1*H*-pyrazol-5-amine **4** in the presence of *p*-toluenesulfonic acid (*p*-TsOH·H₂O) as a catalyst, in good yields at ambient temperature (Scheme 1).

In a pilot experiment, the reaction of *N*-alkyl-3-oxobutanamide **6**, which was prepared by addition of benzylamine **1** to diketene **2**, with benzaldehyde and 1,3-diphenyl-1*H*-pyrazol-5-amine **4** in the presence of *p*-TsOH·H₂O as a catalyst was performed in dry dichloromethane at ambient temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (6 days), the product, *N*-benzyl-6-methyl-1,3,4-triphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide **5a** was obtained in 69% yield.²⁴

We have shown that the use of a wide range of amines **1** and aromatic aldehydes **3** in this four-component reaction makes possible the synthesis of libraries under similar circumstances. Two substituents in the products can be varied independently of each

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Scheme 1.

other. The results are given in Table 1. As anticipated from our initial results, these reactions proceeded very cleanly under mild conditions at room temperature and no undesirable side reactions were observed. All the compounds described herein have been synthesized for the first time.

Aromatic aldehydes possessing both electron-withdrawing and electron-releasing substituents were converted into the corresponding pyrazolo[3,4-*b*]pyridine-5-carboxamide derivatives in good yields. It is noteworthy that the reactions of halo-substituted benzaldehydes gave better yields. For example, 4-bromobenzaldehyde gave the best yield of 76%. We have also examined aliphatic amines to survey the scope and generality of this reaction; thus propylamine was successfully reacted under the same conditions (entry 7).

Compounds **5a–g** were stable solids whose structures were determined by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectra of products **5a–g** displayed molecular ion peaks at appropriate values consistent with the proposed products.

A possible mechanism for the formation of products **5a–g** is shown in Scheme 2. It is rational to assume that intermediate **7** results from initial condensation of the aldehyde **3** with *N*-alkylated-

3-oxobutanamide **6**, derived from the addition of amine **1** to diketene **2**. Next, Michael-type addition of 1,3-diphenyl-1*H*-pyrazol-5-amine **4** to **7** followed by an intramolecular condensation reaction of intermediate **8** gives product **9**. Finally, oxidation of **9** affords the corresponding product **5** (Scheme 2).

In conclusion, we have demonstrated an effective one-pot four-component approach for the synthesis of fully substituted pyrazolo[3,4-*b*]pyridine-5-carboxamide derivatives via cyclocondensation of a primary aliphatic or aromatic amine, diketene, 1,3-diphenyl-1*H*-pyrazol-5-amine and aromatic aldehydes in CH_2Cl_2 using *p*-TsOH· H_2O as the catalyst at ambient temperature. All the products were obtained with high purity and in good yields using very simple and accessible starting materials. We hope to assess this new class of compounds for biological activity.

Acknowledgement

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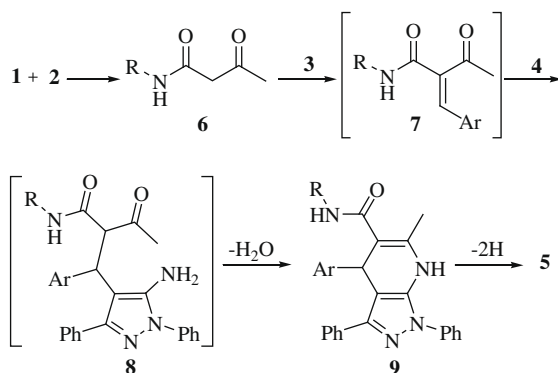
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Table 1
Synthesis of pyrazolo[3,4-*b*]pyridine-5-carboxamides **5a–g**

Entry	R ¹	R ²	Product	Time (days)	Yield ^a (%)
1	C ₆ H ₅ CH ₂	H	5a	6	69
2	C ₆ H ₅ CH ₂	4-Cl	5b	5	71
3	4-CH ₃ C ₆ H ₄	4-Br	5c	4	76
4	4-CH ₃ C ₆ H ₄	4-F	5d	5	71
5	4-CH ₃ C ₆ H ₄	3-Cl	5e	5	74
6	4-CH ₃ C ₆ H ₄	4-CH ₃	5f	7	67
7	<i>n</i> -C ₃ H ₇	4-Cl	5g	6	73

^a Isolated yield.



Scheme 2. A possible mechanism for the formation of **5a–g**.

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24. **Typical procedure for the synthesis of *N*-benzyl-6-methyl-1,3,4-triphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (5a):** A solution of benzylamine (0.107 g, 1.0 mmol) and diketene (0.084 g, 1.0 mmol) was magnetically stirred in 5 mL of dry CH₂Cl₂ for 2 h. Then, benzaldehyde (0.106 g, 1.0 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (0.235 g, 1.0 mmol) and *p*-TsOH·H₂O (0.019 g, 0.1 mmol) were added simultaneously. The reaction mixture was allowed to stir for 6 days until a precipitate appeared. After completion of the reaction, as indicated by TLC (EtOAc/*n*-hexane, 1:2), the precipitate was filtered off, washed with water and then with ethanol and dried in vacuo to give **5a** as a yellow powder (0.34 g, 69%): mp = 224 °C (dec.). IR (KBr) cm⁻¹: 3438, 3260, 3060, 2924, 1634, 1597, 1561, 1497, 1452, 1412. ¹H NMR (500.13 MHz, DMSO-*d*₆) δ: 2.64 (3H, s, CH₃), 4.22 (2H, d, *J* = 5.5 Hz, CH₂), 6.74 (2H, d, *J* = 4.8 Hz, H-Ar), 6.95–7.20 (12H, m, H-Ar), 7.27 (1H, t, *J* = 7.0 Hz, H-Ar), 7.36 (1H, t, *J* = 7.3 Hz, H-Ar), 7.58 (2H, t, *J* = 7.8 Hz, H-Ar), 8.30 (2H, d, *J* = 7.9 Hz, H-Ar), 8.66–8.70 (1H, m, NHCO). ¹³C NMR (125.77 MHz, DMSO-*d*₆) δ: 24.0 (CH₃), 43.1 (CH₂), 112.2, 122.0, 127.1, 127.4, 127.8, 128.2, 128.5, 129.0, 129.5, 129.6, 130.1, 133.0, 135.4, 139.5, 139.9, 143.1, 147.0, 150.4, 156.5 (C-Ar and C=C), 168.0 (CO). MS *m/z*: 495 (M⁺+1, 40), 494 (M⁺, 18), 479 (65), 388 (100), 360 (35), 285 (15), 255 (15), 106 (27), 91 (54), 77 (85), 51 (40). Anal. Calcd for C₃₃H₂₆N₄O: C, 80.14; H, 5.30; N, 11.33. Found: C, 80.11; H, 5.47; N, 11.59.
- Compounds Characterization Data. *N*-Benzyl-4-(4-chlorophenyl)-6-methyl-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (5b):** White powder (0.37 g, 71%): mp = 246–247 °C. IR (KBr) cm⁻¹: 3443, 3265, 3064, 2924, 1640, 1598, 1558, 1454, 1418. ¹H NMR (300.13 MHz, DMSO-*d*₆) δ: 2.68 (3H, s, CH₃), 4.27 (2H, d, *J* = 5.1 Hz, CH₂), 6.78 (2H, d, *J* = 4.0 Hz, H-Ar), 7.01–7.30 (12H, m, H-Ar), 7.40 (1H, t, *J* = 7.3 Hz, H-Ar), 7.61 (2H, t, *J* = 7.8 Hz, H-Ar), 8.32 (2H, d, *J* = 7.9 Hz, H-Ar), 8.78 (1H, t, *J* = 5.6 Hz, NHCO). ¹³C NMR (75.47 MHz, DMSO-*d*₆) δ: 23.6 (CH₃), 42.7 (CH₂), 111.8, 121.6, 126.8, 127.1, 127.4, 127.9, 128.3, 128.4, 128.9, 129.3, 129.7, 131.4, 132.4, 133.7, 133.8, 139.0, 139.3, 141.4, 146.4, 149.9, 156.2 (C-Ar and C=C), 167.4 (CO). MS *m/z*: 530 (M⁺, ³⁷Cl, 10), 528 (M⁺, ³⁵Cl, 13), 513 (72), 422 (100), 396 (37), 296 (50), 106 (70), 91 (70), 77 (78), 51 (40). Anal. Calcd for C₃₃H₂₅ClN₄O: C, 74.92; H, 4.76; N, 10.59. Found: C, 74.83; H, 4.87; N, 10.36.
- N*-(4-Methylbenzyl)-4-(4-bromophenyl)-6-methyl-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (5c):** Yellow powder (0.43 g, 76%): mp = 235 °C (dec.). IR (KBr) cm⁻¹: 3451, 3273, 3050, 2924, 1637, 1557, 1501. ¹H NMR (500.13 MHz, DMSO-*d*₆) δ: 2.21 (3H, s, CH₃), 2.63 (3H, s, CH₃), 4.17 (2H, br s, CH₂), 6.53–7.63 (16H, m, H-Ar), 8.28 (2H, br s, H-Ar), 8.68 (1H, br s, NHCO). ¹³C NMR (125.77 MHz, DMSO-*d*₆) δ: 21.6, 24.0 (CH₃), 42.9 (CH₂), 122.0, 122.9, 127.1, 127.8, 128.3, 128.6, 129.3, 129.7, 130.1, 131.2, 132.0, 132.8, 134.4, 136.4, 139.8, 146.8, 156.6 (C-Ar and C=C), 167.7 (CO). MS *m/z*: 588 (M⁺, ⁸¹Br, 10), 586 (M⁺, ⁷⁹Br, 9), 573 (26), 460 (28), 440 (28), 387 (26), 255 (10), 214 (10), 120 (76), 105 (58), 77 (100), 51 (45). Anal. Calcd for C₃₄H₂₇BrN₄O: C, 69.51; H, 4.63; N, 9.54. Found: C, 69.41; H, 4.55; N, 9.67.
- N*-(4-Methylbenzyl)-4-(4-fluorophenyl)-6-methyl-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (5d):** Yellow powder (0.37 g, 71%): mp = 240 °C (dec.). IR (KBr) cm⁻¹: 3451, 3270, 3058, 2927, 1635, 1599, 1560, 1504, 1410. ¹H NMR (300.13 MHz, DMSO-*d*₆) δ: 2.06 (3H, s, CH₃), 2.66 (3H, s, CH₃), 4.19 (2H, br s, CH₂), 6.60–7.65 (16H, m, H-Ar), 8.30 (2H, br s, H-Ar), 8.72 (1H, br s, NHCO). ¹³C NMR (75.47 MHz, DMSO-*d*₆) δ: 21.1, 23.6 (CH₃), 42.4 (CH₂), 111.9, 114.7, 115.0, 121.6, 126.7, 127.4, 127.9, 128.3, 129.0, 129.2, 129.3, 129.7, 131.7, 131.8, 132.5, 136.0, 139.3, 141.7, 146.5, 149.9, 156.1 (C-Ar and C=C), 167.4 (CO). MS *m/z*: 526 (M⁺, 32), 511 (60), 406 (85), 380 (36), 273 (12), 120 (70), 105 (50), 77 (100), 51 (43). Anal. Calcd for C₃₄H₂₇FN₄O: C, 77.55; H, 5.17; N, 10.64. Found: C, 77.43; H, 5.01; N, 10.56.
- N*-(4-Methylbenzyl)-4-(3-chlorophenyl)-6-methyl-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (5e):** Yellow powder (0.40 g, 74%): mp = 245 °C (dec.). IR (KBr) cm⁻¹: 3440, 3249, 3055, 2923, 1643, 1555, 1500, 1410. ¹H NMR (500.13 MHz, DMSO-*d*₆) δ: 2.19 (3H, s, CH₃), 2.64 (3H, s, CH₃), 4.18 (2H, d, *J* = 13.3 Hz, CH₂), 6.47–7.87 (16H, m, H-Ar), 8.28 (2H, br s, H-Ar), 8.66 (1H, br s, NHCO). ¹³C NMR (125.77 MHz, DMSO-*d*₆) δ: 21.5 (CH₃), 24.0 (CH₃), 42.9 (CH₂), 122.0, 127.2, 127.7, 128.3, 128.6, 128.8, 129.0, 129.2, 129.5, 130.1, 132.8, 136.3, 139.7, 146.8, 150.3, 156.7 (C-Ar and C=C), 167.7 (CO). MS *m/z*: 544 (M⁺, ³⁷Cl, 6), 542 (M⁺, ³⁵Cl, 14), 527 (25), 464 (14), 422 (50), 396 (45), 120 (80), 105 (50), 77 (100), 51 (48). Anal. Calcd for C₃₄H₂₇ClN₄O: C, 75.20; H, 5.01; N, 10.32. Found: C, 75.23; H, 5.06; N, 10.36.
- N*-(4-Methylbenzyl)-6-methyl-1,3-diphenyl-4-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (5f):** Yellow powder (0.35 g, 67%): mp = 250 °C (dec.). IR (KBr) cm⁻¹: 3243, 3062, 2920, 1635, 1560, 1499, 1441, 1413. ¹H NMR (500.13 MHz, DMSO-*d*₆) δ: 2.20 (3H, s, CH₃), 2.25 (3H, s, CH₃), 2.62 (3H, s, CH₃), 4.17 (2H, d, *J* = 5.4 Hz, CH₂), 6.67 (2H, d, *J* = 7.5 Hz, H-Ar), 6.82–7.05 (10H, m, H-Ar), 7.17 (1H, t, *J* = 6.7 Hz, H-Ar), 7.35 (1H, t, *J* = 7.2 Hz, H-Ar), 7.57 (2H, t, *J* = 7.6 Hz, H-Ar), 8.30 (2H, d, *J* = 8.0 Hz, H-Ar), 8.63 (1H, t, *J* = 5.5 Hz, NHCO). ¹³C NMR (125.77 MHz, DMSO-*d*₆) δ: 21.5 (CH₃), 21.7 (CH₃), 24.0 (CH₃), 42.9 (CH₂), 112.4, 122.0, 126.4, 127.0, 127.9, 128.1, 128.4, 128.8, 129.4, 129.5, 129.6, 129.9, 130.1, 132.5, 133.0, 136.4, 136.5, 138.5, 139.9, 143.3, 147.0, 150.4, 156.5 (C-Ar and C=C), 168.0 (CO). MS *m/z*: 522 (M⁺, 30), 507 (75), 402 (100), 374 (42), 299 (12), 255 (14), 120 (50), 105 (55), 77 (80), 51 (60). Anal. Calcd for C₃₅H₃₀N₄O: C, 80.43; H, 5.79; N, 10.72. Found: C, 80.33; H, 5.71; N, 10.66.
- 4-(4-Chlorophenyl)-6-methyl-1,3-diphenyl-*N*-propyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (5g):** Yellow powder (0.35 g, 73%): mp = 259–261 °C. IR (KBr) cm⁻¹: 3449, 3285, 3070, 2921, 1641, 1551, 1499, 1408. ¹H NMR (300.13 MHz, DMSO-*d*₆) δ: 0.56 (3H, t, *J* = 7.0 Hz, CH₃), 1.04–1.20 (2H, m, CH₂), 2.64 (3H, s, CH₃), 2.83–2.97 (2H, m, CH₂), 6.97–7.28 (9H, m, H-Ar), 7.36 (1H, t, *J* = 6.8 Hz, H-Ar), 7.57 (2H, t, *J* = 7.1 Hz, H-Ar), 8.19–8.27 (2H, m, H-Ar), 8.28 (1H, d, *J* = 7.6 Hz, NHCO). ¹³C NMR (75.47 MHz, DMSO-*d*₆) δ: 12.0 (CH₃), 22.7 (CH₂), 24.0 (CH₃), 41.4 (CH₂), 112.1, 122.0, 127.1, 128.1, 128.3, 128.7, 129.7, 130.1, 131.7, 132.9, 134.1, 134.2, 139.8, 141.8, 146.8, 150.3, 156.6 (C-Ar and C=C), 167.6 (CO). MS *m/z*: 482 (M⁺, ³⁷Cl, 25), 480 (M⁺, ³⁵Cl, 65), 465 (15), 438 (25), 422 (85), 386 (15), 344 (12), 255 (14), 211 (11), 179 (15), 77 (100), 51 (50). Anal. Calcd for C₂₉H₂₅ClN₄O: C, 72.42; H, 5.24; N, 11.65. Found: C, 72.53; H, 5.27; N, 11.36.