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Multicomponent Strategy for the Preparation of Pyrrolo[1,2-*a*]-pyrimidine Derivatives under Catalyst-Free and Microwave Irradiation Conditions

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A simple and efficient one-pot procedure has been developed for the construction of pyrrolo[1,2-*a*]pyrimidines via the three-component domino reaction of 5-aminopyrazoles, acetylenedicarboxylates and malononitrile under catalyst-free, microwave irradiation conditions. The key step in this transformation is the N—N bond cleavage reaction of the 5-aminopyrazole substrate, which has been reported in this context for the first time in this study. The advantages of this protocol include readily available starting materials, short reaction times and good regioselectivity.

Keywords pyrrolo[1,2-*a*]pyrimidine derivatives, multi-component reactions, catalyst-free, microwave irradiation

Introduction

Pyrrolopyrimidines are an important class of nitrogen-containing heterocyclic skeletons, which have been reported to exhibit a variety of interesting biological activities,[1] including anti-HIV, anti-HCV and anti-HSV activities, as well as inhibitory activities towards aurora-A kinase and cAMP phosphodiesterase.[2] In light of their interesting biological properties, a variety of different methods have been developed for the construction of compounds belonging to this important structural class.[3] However, these methods generally suffer from limitations such as low yields, the limited availability of suitable starting materials, and their requirement for multistage synthetic procedures. The development of convenient and efficient methods for the synthesis of pyrrolopyrimidines from simple and readily available starting materials is therefore highly desired in organic chemistry.[4]

Several convenient and efficient strategies have been developed during the last decade for the construction of a diverse range of complex heterocycles.[5] Multicomponent reactions (MCRs),[6] where three of more components are combined in a single synthetic operation to afford increasingly complicated products, are important transformations in synthetic organic chemistry. MCRs have several unique advantages, including their high atom-economy, simple operation, ease of purification and low levels of waste generation.[7] These features have led to the emergence of MCRs as efficient strategies for the construction of a diverse range of complex heterocycles starting with simple materials.[8]

5-Aminopyrazoles have been used as versatile building blocks in numerous MCRs for the rapid construction of various heterocyclic compounds.[9] Previous reports pertaining to the use of this building block in MCRs have mainly focused on the use of these substrates as binucleophilic reagents via their C-4 and NH_2 positions.[10] However, there have been no reports pertaining to MCRs involving 5-aminopyrazoles where the N—N bond of this substrate undergoes a cleavage reaction. In a continuation of our ongoing work towards the development of new MCRs for the construction of heterocyclic compounds,[11] we report, herein, an efficient process for the synthesis of pyrrolo[1,2-*a*]pyrimidine derivatives via the three-component reaction of 5-aminopyrazoles, acetylenedicarboxylates and malononitrile under catalyst-free, microwave irradiation conditions.

Experimental

General experimental methods

All reagents were purchased from commercial suppliers and used without further purification. Melting points were determined using an XT-4 micro melting point apparatus and are uncorrected. IR spectra were recorded with a Varian F-1000 spectrometer using KBr disc. Absorptions are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were obtained in DMSO-d_6 solution, using a Bruker-400 MHz spectrometer. *J* values are re-

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ported in hertz and chemical shifts are expressed in parts per million downfield from TMS as an internal standard. HRMS analyses were carried out using a Bruker micrOTOF-QII instrument. Microwave irradiation experiments were conducted in an Initiator 2.5 Microwave system (Biotage, Uppsala, Sweden). The reaction temperatures were measured using an infrared detector (external sensor type) during the microwave heating stages.

General experimental procedure

A mixture of a 5-aminopyrazole **1** (1.0 mmol), an acetylenedicarboxylate **2** (1.0 mmol), a malononitrile **3** (1.0 mmol) and an acetonitrile (4.0 mL) was placed in a 5-mL initiator reaction vial, which was sealed and stirred for 15 s at room temperature. The vial was then heated for 20 min at 110 ℃ under microwave irradiation (absorption level, high; fixed hold time). Upon completion of the reaction, as determined by TLC using a 3∶1 (*V*/*V*) mixture of petroleum ether and ethyl acetate as the development solvent, the microwave irradiation process was suspended and the reaction mixture was cooled to room temperature. The reaction solvent was subsequently removed *in vacuo* to give a residue, which was purified by column chromatography over silica gel eluting with a mixture of ethyl acetate and petroleum ether to afford the desired products **4** and **5**.

Dimethyl 2-amino-8-cyano-4-methylpyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (4a) White solid, yield 76%, m.p. 290－293 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.50 (s, 2H, NH_2), 6.32 (s, 1H, CH), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 162.6, 158.0, 148.9, 145.2, 119.8, 116.3, 115.6, 104.0, 74.9, 53.8, 52.9, 19.1; IR (KBr) *v*: 3191, 2214, 1657, 1535, 1427, 1370, 1368, 1333, 1224, 1099, 869, 683 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{11}N_4O_4$ [$(M-H)^-$] 287.0780, found 287.0781.

Dimethyl 8-cyano-4-methyl-2-(phenylamino)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5a) Yellow solid, yield 12%, m.p. 241－242 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H, NH), 7.85 (d, J=8.0 Hz, 2H, ArH), 7.38 (t, J=7.8 Hz, 2H, ArH), 7.09 (t, J=7.2 Hz, 1H, ArH), 6.58 (s, 1H, CH), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.7, 162.4, 153.6, 147.4, 145.2, 139.8, 129.3, 123.6, 120.1, 119.6, 117.2, 115.1, 105.2, 77.0, 54.0, 53.0, 19.2; IR (KBr) *v*: 3351, 2218, 1709, 1650, 1560, 1520, 1232, 1181, 1092, 757, 692 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{15}N_4O_4$ [$(M-H)^-$] 363.1093, found 363.1091.

Diethyl 2-amino-8-cyano-4-methylpyrrolo[1,2-*a*]-pyrimidine-6,7-dicarboxylate (4b) White solid, yield 73%, m.p. 211 － 213 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.48 (s, 2H, NH_2), 6.31 (s, 1H, CH), 4.33 －4.27 (m, 4H, 2×CH_2), 2.40 (s, 3H, CH_3), 1.32－1.25 (m, 6H, 2×CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.2, 162.1, 157.9, 148.7, 145.2, 119.8, 116.5, 115.5, 103.9, 74.9, 62.9, 61.6, 19.1, 14.3, 14.0; IR (KBr) *v*: 3437, 3196, 2210, 1714, 1660, 1520, 1479, 1215, 1097, 769, 686 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{15}N_4O_4$ [$(M-H)^-$] 315.1093, found 315.1078.

Diethyl 8-cyano-4-methyl-2-(phenylamino)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5b) Yellow solid, yield 17%, m.p. 130－132 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.05 (s, 1H, NH), 7.85 (d, J=8.0 Hz, 2H, ArH), 7.37 (t, J=8.0 Hz, 2H, ArH), 7.08 (t, J=7.2 Hz, 1H, ArH), 6.56 (s, 1H, CH), 4.38－4.28 (m, 4H, 2×CH_2), 2.47 (s, 3H, CH_3), 1.34－1.27 (m, 6H, 2×CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.2, 161.9, 153.5, 147.3, 145.2, 139.8, 129.3, 123.6, 120.1, 119.7, 117.4, 115.1, 105.1, 77.1, 63.1, 61.7, 19.2, 14.3, 14.0; IR (KBr) *v*: 3431, 3213, 2224, 1718, 1693, 1519, 1441, 1300, 1195, 1089, 891, 667 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{19}N_4O_4$ [$(M-H)^-$] 391.1406, found 391.1426.

Dimethyl 2-amino-8-cyano-4-phenylpyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (4c). Yellow solid, yield 69%, m.p. 238－240 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.65 (s, 2H, NH_2), 7.55－7.49 (m, 5H, ArH), 6.33 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 3.11 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.5, 165.4, 163.1, 154.3, 151.8, 137.7, 135.8, 134.1, 132.8, 125.5, 121.3, 120.5, 110.1, 80.4, 57.8, 57.4; IR (KBr) *v*: 3151, 2213, 1718, 1651, 1537, 1497, 1443, 1335, 1221, 1102, 849, 765, 672 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{13}N_4O_4$ [$(M-H)^-$] 349.0937, found 349.0926.

Dimethyl 8-cyano-2-(methylamino)-4-phenylpyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5c) White solid, yield 19%, m.p. 249－250 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.10－8.06 (m, 1H, NH), 7.55－7.46 (m, 5H, ArH), 6.32 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 3.11 (s, 3H, OCH_3), 2.94 (d, J=4.4 Hz, 3H, NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.5, 160.5, 156.7, 149.3, 145.7, 132.6, 130.8, 129.2, 128.0, 126.9, 120.2, 116.7, 115.6, 105.7, 52.8, 52.4, 27.7; IR (KBr) *v*: 3347, 2221, 1735, 1649, 1537, 1420, 1397, 1252, 1184, 1104, 765, 703 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{16}N_4NaO_4$ [$(M+Na)^+$] 387.1069, found 387.1061.

Diethyl 2-amino-8-cyano-4-phenylpyrrolo[1,2-*a*]-pyrimidine-6,7-dicarboxylate (4d) Yellow solid, yield 63%, m.p. 192－194 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.63 (s, 2H, NH_2), 7.55－7.49 (m, 5H, ArH), 6.32 (s, 1H, CH), 4.24 (q, J=7.2 Hz, 2H, OCH_2), 3.43 (q, J=7.2 Hz, 2H, OCH_2), 1.23 (t, J=7.2 Hz, 3H, CH_3), 1.00 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.1, 160.0, 158.1, 149.2, 146.9, 132.8, 130.8, 129.1, 127.9, 120.9, 116.4, 115.5, 105.2, 75.5, 61.7, 61.6, 14.2, 13.8; IR (KBr) *v*: 3449, 3149, 2213, 1714, 1662, 1528, 1461, 1378, 1252, 1101, 849, 762, 698 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{17}N_4O_4$ [$(M-H)^-$] 377.1250, found 377.1257.

Diethyl 8-cyano-2-(methylamino)-4-phenylpyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5d) White solid, yield 21%, m.p. 134－136 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.08－8.05 (m, 1H, NH), 7.54－

7.495 (m, 5H, ArH), 6.31 (s, 1H, CH), 4.24 (q, J=7.2 Hz, 2H, OCH_2), 3.43 (q, J=7.2 Hz, 2H, OCH_2), 2.94 (d, J=4.4 Hz, 3H, NCH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3), 1.01 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.1, 160.1, 156.7, 149.2, 145.8, 132.7, 130.8, 129.1, 128.0, 120.4, 116.7, 115.5, 105.7, 76.1, 61.8, 61.6, 27.7, 14.3, 13.8; IR (KBr) v: 3197, 2212, 1721, 1416, 1385, 1217, 1185, 1135 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{20}N_4NaO_4$ [(M+Na)$^+$] 415.1382, found 415.1387.

Dimethyl 8-cyano-4-methyl-2-(methylamino)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5e) White solid, yield 11%, m.p. 196−198 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.99−7.96 (s, 1H, NH), 6.32 (s, 1H, CH), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.88 (d, J=4.8 Hz, 3H, NCH_3), 2.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.8, 162.6, 156.6, 148.8, 143.9, 119.2, 116.6, 115.6, 104.4, 75.4, 53.8, 52.8, 27.4, 18.8; IR (KBr) v: 3121, 2216, 1734, 1643, 1480, 1384, 1184, 1092, 846 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{14}N_4NaO_4$ [(M+Na)$^+$] 325.0907, found 325.0905.

Diethyl 8-cyano-4-methyl-2-(methylamino)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5f) White solid, yield 9%, m.p. 138−140 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.97−7.93 (m, 1H, NH), 6.31 (s, 1H, CH), 4.35−4.26 (m, 4H, 2×CH_2), 2.88 (d, J=4.8 Hz, 3H, NCH_3), 2.39 (s, 3H, CH_3), 1.32−1.26 (m, 6H, 2×CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.3, 162.0, 156.4, 148.7, 143.9, 119.3, 116.8, 115.6, 104.4, 75.6, 62.9, 61.6, 27.5, 18.9, 14.3, 14.0; IR (KBr) v: 3411, 2215, 1704, 1584, 1440, 1385, 1225, 1159, 1088, 858, 688 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{18}N_4NaO_4$ [(M+Na)$^+$] 353.1226, found 353.1219.

Dimethyl 8-cyano-4-phenyl-2-(phenylamino)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5g) Yellow solid, yield 14%, m.p. 233−235 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.19 (s, 1H, NH), 7.89 (d, J=8.0 Hz, 2H, ArH), 7.59−7.56 (m, 5H, ArH), 7.41 (t, J=8.0 Hz, 2H, ArH), 7.12 (t, J=7.2 Hz, 1H, ArH), 6.59 (s, 1H, CH), 3.81 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.3, 160.4, 153.6, 147.9, 146.7, 139.6, 132.4, 131.0, 129.4, 129.2, 128.0, 127.1, 123.8, 120.0, 117.3, 115.1, 106.5, 77.5, 52.9, 52.6; IR (KBr) v: 3467, 2221, 1731, 1560, 1537, 1426, 1256, 993, 672 cm^{-1}. HRMS (ESI) calcd for $C_{24}H_{17}N_4O_4$ [(M–H)$^-$] 425.1250, found 425.1250.

Diethyl 8-cyano-4-phenyl-2-(phenylamino)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5h) Yellow solid, yield 12%, m.p. 190−192 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.18 (s, 1H, NH), 7.89 (d, J=8.0 Hz, 2H, ArH), 7.57−7.54 (m, 5H, ArH), 7.41 (t, J=7.6 Hz, 2H, ArH), 7.11 (t, J=7.2 Hz, 1H, ArH), 6.58 (s, 1H, CH), 4.27 (q, J=7.2 Hz, 2H, OCH_2), 3.47 (q, J=7.2 Hz, 2H, OCH_2), 1.25 (t, J=7.2 Hz, 3H, CH_3), 1.03 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.9, 160.0, 153.6, 147.9, 146.7, 139.7, 132.6, 131.0, 129.4, 129.2, 128.1, 123.8, 120.8, 120.1, 117.4, 115.1, 106.6, 77.7, 62.0, 61.7, 14.3, 13.8; IR (KBr) v: 3357, 2984, 1715, 1569, 1492, 1329, 1296, 891, 696 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{21}N_4O_4$ [(M–H)$^-$] 453.1563, found 453.1582.

Dimethyl 2-amino-8-cyano-4-cyclopropylpyrrolo-[1,2-*a*]pyrimidine-6,7-dicarboxylate (4i) Yellow solid, yield 72%, m.p. 250−252 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.44 (s, 2H, NH_2), 6.30 (s, 1H, CH), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.02−1.95 (m, 1H, CH), 0.98−0.93 (m, 2H, CH_2), 0.77−0.73 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.9, 162.6, 158.2, 149.0, 148.6, 118.9, 117.1, 115.6, 102.4, 75.0, 53.7, 52.8, 13.3, 7.4; IR (KBr) v: 3152, 2949, 1719, 1536, 1449, 1342, 1252, 874, 785, 685 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{14}N_4NaO_4$ [(M+Na)$^+$] 337.0913, found 337.0907.

Dimethyl 8-cyano-4-cycloprpopyl-2-(phenylamino)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5i) Yellow solid, yield 13%, m.p. 194−195 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.01 (s, 1H, NH), 7.85 (d, J=7.6 Hz, 2H, ArH), 7.38 (t, J=7.6 Hz, 2H, ArH), 7.08 (t, J=7.6 Hz, 1H, ArH), 6.56 (s, 1H, CH), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.06−2.02 (m, 1H, CH), 1.02−1.00 (m, 2H, CH_2), 0.82−0.80 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.8, 162.4, 153.7, 148.8, 147.2, 139.8, 129.4, 123.6, 119.8, 118.9, 117.9, 115.2, 103.9, 77.2, 53.9, 53.0, 13.4, 7.6; IR (KBr) v: 3343, 2946, 1720, 1623, 1571, 1450, 1384, 1234, 1020, 922, 692 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{18}N_4NaO_4$ [(M+Na)$^+$] 413.1226, found 413.1217.

Diethyl 2-amino-8-cyano-4-cyclopropylpyrrolo-[1,2-*a*]pyrimidine-6,7-dicarboxylate (4j) White solid, yield 69%, m.p. 180−182 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.43 (s, 2H, NH_2), 6.29 (s, 1H, CH), 4.33−4.26 (m, 4H, 2×CH_2), 2.04−1.98 (m, 1H, CH), 1.31−1.26 (m, 6H, 2×CH_3), 0.97−0.94 (m, 2H, CH_2), 0.78 − 0.74 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.3, 162.1, 158.1, 149.0, 148.6, 119.2, 117.1, 115.6, 102.3, 75.1, 62.8, 61.6, 14.4, 14.1, 13.3, 7.6; IR (KBr) v: 2988, 2214, 1718, 1656, 1528, 1458, 1302, 1219, 1151, 1094, 1028, 680 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{18}N_4NaO_4$ [(M+Na)$^+$] 365.1226, found 365.1227.

Diethyl 8-cyano-4-cyclopropyl-2-(phenylamino)-pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5j) Yellow solid, yield 12%, m.p. 192−194 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.99 (s, 1H, NH), 7.85 (d, J=8.0 Hz, 2H, ArH), 7.37 (t, J=7.6 Hz, 2H, ArH), 7.07 (t, J=7.6 Hz, 1H, ArH), 6.55 (s, 1H, CH), 4.37−4.28 (m, 4H, 2×CH_2), 2.10−2.03 (m, 1H, CH), 1.33−1.28 (m, 6H, 2×CH_3), 1.03−1.00 (m, 2H, CH_2), 0.84−0.82 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.3, 161.9, 153.6, 148.9, 147.1, 139.8, 129.4, 123.5, 119.8, 119.2, 117.9, 115.2, 103.8, 77.4, 63.0, 61.7, 14.4, 14.1, 13.4, 7.7; IR (KBr) v: 3347, 2982, 2213, 1714, 1622, 1572, 1410, 1383, 1096, 1032, 763, 693 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{22}N_4NaO_4$ [(M+Na)$^+$ 441.1539, found 441.1527.

Dimethyl 8-cyano-4-cyclopropyl-2-(methylami-

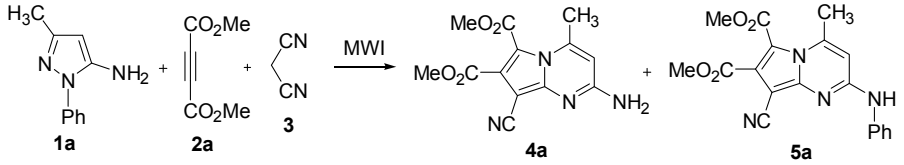
no)pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5k) Yellow solid, yield 12%, m.p. 213—215 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.88—7.85 (m, 1H, NH), 6.29 (s, 1H, CH), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.88 (d, J=4.8 Hz, 3H, NCH_3), 2.00—1.94 (m, 1H, CH), 0.97—0.93 (m, 2H, CH_2), 0.75—0.71 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.9, 162.5, 156.8, 148.6, 147.8, 118.6, 117.3, 115.7, 103.0, 75.7, 53.8, 52.8, 27.6, 13.2, 7.4; IR (KBr) v: 3393, 2925, 1710, 1658, 1536, 1443, 1325, 1180, 1001, 813, 765, 684 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{16}N_4NaO_4$ [$(M+Na)^+$] 351.1069, found 351.1051.

Diethyl 8-cyano-4-cyclopropyl-2-(methylamino)-pyrrolo[1,2-*a*]pyrimidine-6,7-dicarboxylate (5l) Yellow solid, yield 11%, m.p. 184—186 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.87—7.84 (m, 1H, NH), 6.28 (s, 1H, CH), 4.34—4.26 (m, 4H, 2×CH_2), 2.88 (d, J=4.8 Hz, 3H, NCH_3), 2.08—1.96 (m, 1H, CH), 1.31—1.26 (m, 6H, 2×CH_3), 0.98—0.93 (m, 2H, CH_2), 0.75—0.74 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.4, 162.1, 156.8, 148.5, 147.9, 118.9, 117.3, 115.6, 102.9, 75.8, 62.8, 61.5, 27.6, 14.4, 14.1, 13.2, 7.6; IR (KBr) v: 3445, 2985, 1715, 1595, 1445, 1385, 1218, 1129, 1104, 1025, 836, 685 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{20}N_4NaO_4$ [$(M+Na)^+$] 379.1382, found 379.1386.

Results and Discussion

Initially, we selected the three-component reaction of 5-amino-3-methyl-1-phenylpyrazole (**1a**) with dimethyl but-2-ynedioate (**2a**) and malononitrile (**3**) as a model reaction for optimizing the reaction conditions (Table 1). When the reaction was carried out in methanol at 100 ℃ for 10 min under microwave irradiation and catalyst-free conditions, compound **4a** was obtained in 13% yield, without any of the other product **5a** (Table 1, Entry 1). Various solvents were subsequently evaluated in this reaction to determine the impact of the solvent on the yield, and the results revealed that acetonitrile gave the best result (Table 1, Entries 1—7). We also evaluated the influence of the reaction time (Table 1, Entries 7—9) and reaction temperature (Table 1, Entries 8 and 10—15) on the outcome of the reaction. The results revealed that the optimum reaction time and reaction temperature were 20 min and 110 ℃, respectively. Several catalysts, including acidic (H_2SO_4 and

Table 1 Optimization of the reaction conditions for synthesis of **4** and **5** under microwave irradiation conditions[a]



Entry	Solvent	Catalyst/mol%	Temperature/℃	Time/min	Yield[b]/%	
					4a	**5a**
1	MeOH	—	100	10	13	trace
2	EtOH	—	100	10	32	12
3	DMF	—	140	10	trace	7
4	DMSO	—	140	10	22	16
5	Toluene	—	110	10	0	0
6	$HO(CH_2)_2OHOH$	—	140	10	28	19
7	CH_3CN	—	100	10	38	4
8	CH_3CN	—	100	20	65	11
9	CH_3CN	—	100	30	57	9
10	CH_3CN	—	60	20	23	2
11	CH_3CN	—	70	20	46	4
12	CH_3CN	—	80	20	47	4
13	CH_3CN	—	90	20	54	6
14	CH_3CN	—	110	20	76	12
15	CH_3CN	—	120	20	75	9
16	CH_3CN	H_2SO_4 (20)	110	20	49	13
17	CH_3CN	TsOH (20)	110	20	19	6
18	CH_3CN	NaOH (20)	110	20	38	7
19	CH_3CN	CuCl (20)	110	20	36	22
20	CH_3CN	*L*-Proline (20)	110	20	38	28

[a] Reactions were performed using **1a** (1.0 mmol), **2a** (1.0 mmol) and **3** (1.0 mmol) in solvent (4.0 mL) under microwave irradiation conditions. [b] Isolated yields.

TsOH), basic (NaOH), metal (CuCl) and organic (such as *L*-proline) catalysts were also evaluated in terms of their impact on the yield of this transformation. However, none of these catalysts led to an improvement in the yield of the reaction (Table 1, Entries 16—20). Based on these screening experiments, the optimum reaction conditions for the formation of **4a** were determined to be acetonitrile at 110 ℃ for 20 min under microwave irradiation and catalyst-free conditions (Table 1, Entry 14).

With the optimum reaction conditions in hand, we proceeded to evaluate the scope of the transformation using a variety of different substituted 5-aminopyrazoles **1** and acetylenedicarboxylates **2** (Table 2). As shown in Table 2, methyl, phenyl and cyclopropyl substituents were well tolerated at the R^2 position of the pyrazole ring, with the corresponding products being formed in good yields under the optimized reaction conditions. Furthermore, the R^3 group on the acetylenedicarboxylate substrate could be a methyl or ethyl group, with the final products being isolated in satisfactory yields. It is noteworthy that the yields for product **4** were higher than those of product **5** in all cases for this transformation, highlighting the regioselective nature of this reaction.

The structures of the products were determined by IR, $^1H/^{13}C$ NMR and HRMS analyses. The structures of compounds **4b** and **5a** were confirmed by X-ray crystallographic analysis (Figure 1 and 2).[12,13]

Based on the results, we have studied the mechanism for this three-component transformation. Usually, the amino group of 5-aminopyrazole would add firstly to the acetylenedicarboxylate. However, when the addition product (**6**) was reacted with malononitrile (**3**) under the same reaction conditions, the desired products were not obtained (Scheme 1). Then *N*-acetoaminopyrazole (**7**),

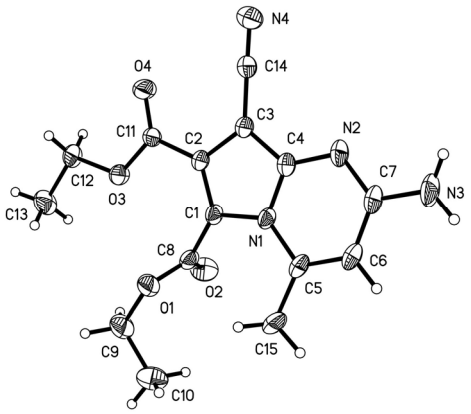


Figure 1 ORTEP diagram of compound **4b**.

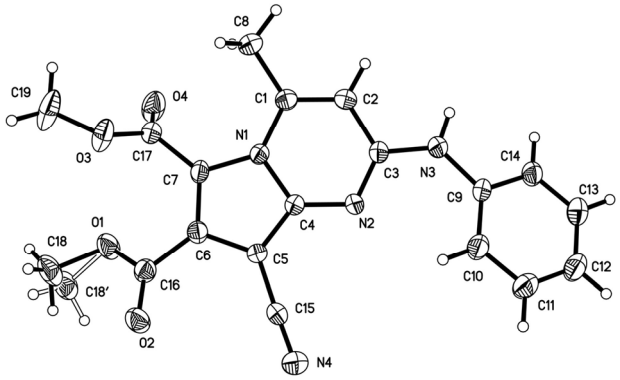
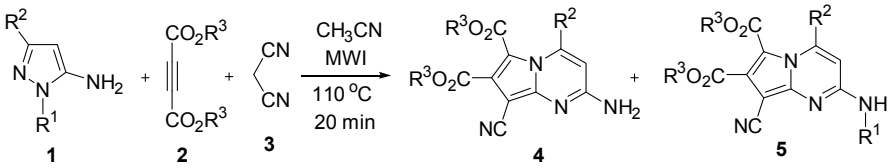


Figure 2 ORTEP diagram of compound **5a**.

Table 2 Synthesis of pyrrolo[1,2-*a*]pyrimidine derivatives under microwave irradiation conditions

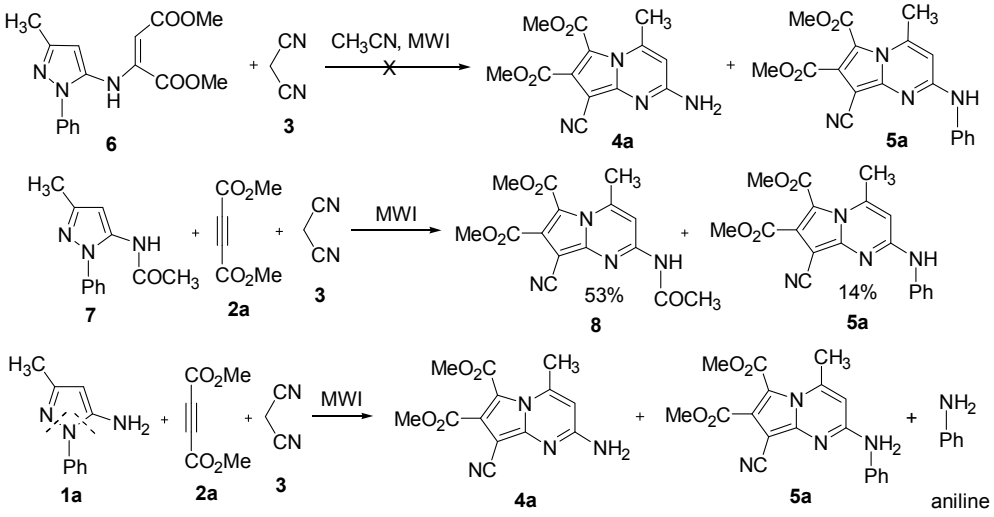


Entry	R^1	R^2	R^3	Isolated yield/%		Isolated yield/%	
				Product	Yield	Product	Yield
1	Ph	CH_3	CH_3	**4a**	76	**5a**	12
2	Ph	CH_3	C_2H_5	**4b**	73	**5b**	17
3	CH_3	Ph	CH_3	**4c**	69	**5c**	19
4	CH_3	Ph	C_2H_5	**4d**	63	**5d**	21
5	CH_3	CH_3	CH_3	**4a**	81	**5e**	11
6	CH_3	CH_3	C_2H_5	**4b**	78	**5f**	9
7	Ph	Ph	CH_3	**4c**	72	**5g**	14
8	Ph	Ph	C_2H_5	**4d**	71	**5h**	12
9	Ph	*c*-Propyl	CH_3	**4i**	72	**5i**	13
10	Ph	*c*-Propyl	C_2H_5	**4j**	69	**5j**	12
11	CH_3	*c*-Propyl	CH_3	**4i**	73	**5k**	12
12	CH_3	*c*-Propyl	C_2H_5	**4j**	66	**5l**	11

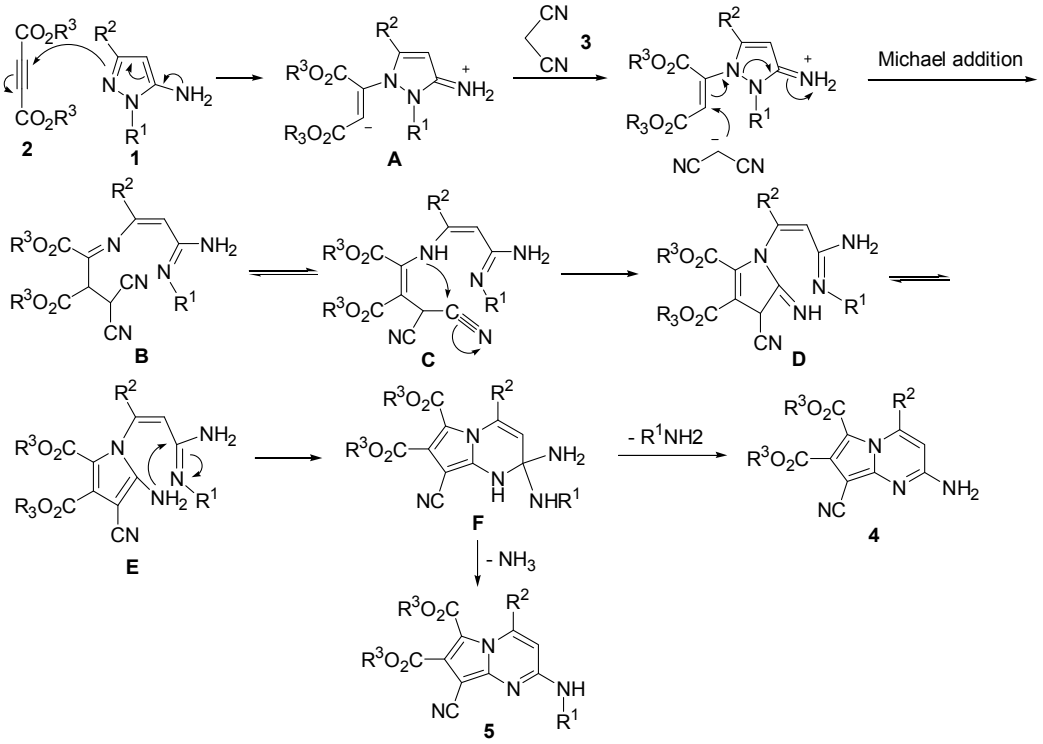
which would not add to acetylenedicarboxylate, was used as material, the desired products **8** and **5a** were obtained in 53% and 14% yields, respectively. These results indicated that the amino group of 5-aminopyrazole did not add firstly to the acetylenedicarboxylate. When 5-amino-3-methyl-1-phenylpyrazole (**1a**), dimethyl but-2-ynedioate (**2a**) and malononitrile (**3**) were carried out under the reaction conditions, in the reaction solution, we detected aniline using HPLC-MS. This result indicated that in this reaction N—N and N—C bonds of the 5-aminopyrazole substrate have been cleavaged.

According to the control experimental studies, we have proposed a mechanism for this novel three-component transformation, which is shown in Scheme 2. The Michael addition of 5-aminopyrazole **1** (through its 2-position) to acetylenedicarboxylate **2** would give intermediate **A**, which would abstract a proton from malononitrile before undergoing sequential Michael addition and tautomerization reactions to give intermediate **B**. Intermediate **B** then undergoes sequential intramolecular nucleophilic addition and tautomerization reaction to form intermediate **E**, which would undergo a second intramolecular nucleophilic addition reaction to form intermediate **F**. Finally, intermediate **F** would lose a molecule of amine (R^1NH_2 or NH_3) to give the desired product **4** or **5**.

Scheme 1 Control experimental studies



Scheme 2 Proposed mechanism for the synthesis of compounds **4** and **5**



Conclusions

In conclusion, we have successfully developed an efficient, three-component reaction for the construction of pyrrolo[1,2-*a*]pyrimidine skeletons under microwave irradiation and catalyst-free conditions. The key feature of this new method is the N—N bond cleavage reaction of the 5-aminopyrazole substrate. This work represents the first reported use of 5-aminopyrazole as a substrate in an MCR of this type.

Acknowledgement

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[12] The single-crystal growth of compounds **4b** and **5a** was carried out in co-solvent of EtOH and DMF at room temperature. Crystal data for **4b**: $C_{15}H_{16}N_4O_4$, crystal dimension 0.45 mm×0.28 mm×0.21 mm, triclinic, space group *P*-1, a=7.7414(7) Å, b=8.8274(8) Å, c=11.8761(9) Å, α=87.385(2)°, β=80.5140(10)°, γ=71.8460(10)°, V=760.61(11) Å^3, M_r=316.32, Z=2, λ=0.71073 Å, μ(MoKα)=0.103 mm^{-1}, F(000) = 332, R_1 = 0.0556. Crystal data for **5a**: $C_{19}H_{16}N_4O_4$, crystal dimension 0.37 mm×0.19 mm×0.10 mm, triclinic, space group *P*-1, a=7.8070(6) Å, b=10.4239(9) Å, c=11.7592(11) Å, α=91.6300(10)°, β=104.984(2)°, γ=109.972(2)°, V=861.61(13) Å^3, M_r=364.36, Z=2, λ=0.71073 Å, μ(MoKα)=0.101 mm^{-1}, F(000)=380, R_1=0.0526.

[13] Crystallographic data for the structures of compounds **4b** and **5a** have been deposited at the Cambridge Crystallographic Data Centre, deposit numbers are CCDC-1473312 and CCDC-1446734, respectively. Copies of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

(Cheng, F.)

