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One-Pot Four-Component Synthesis of Multi-Substituted Pyrano[2,3-*c*] Pyrazole under Ionic Liquid [Bmim]BF_4 Catalysis

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Abstract

A series of multi-substituted pyrano[2,3-*c*]pyrazole derivatives were synthesized by one-pot reaction of ethyl propionyl acetate, phenylhydrazine, aromatic aldehyde and malononitrile. We developed an efficient and convenient method for the synthesis of multi-substituted pyrano[2,3-c]pyrazoles in high yields using ionic liquid [Bmim]BF_4 as a catalyst. And structures of the products were characterized by IR, ^{1}H NMR and MS.

Keywords

Multi-Component Reaction, Multi-Substituted Pyrano[2,3-*c*]pyrazole, One-Pot Synthesis, Ionic Liquid

多取代吡喃[2,3-*c*]吡唑类化合物的在离子液体[Bmim]BF_4催化下的四组分一锅法合成

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摘　要

本文报道了在离子液体[Bmim]BF_4催化下以丙酰乙酸甲酯或丙酰乙酸乙酯，苯肼，芳醛和丙二腈等四组分为原料经过一锅法合成了一系列多取代吡喃[2,3-*c*]吡唑类化合物的方法。该方法具有方便，产率较高等特点，为合成此类化合物提供了一个参考依据。产物的结构通过IR，^{1}H NMR和MS进行表征。

关键词

多组分反应，多取代吡喃[2,3-*c*]吡唑类化合物，一锅法合成，离子液体

1. 引言

多组分反应(MCRs)是从三个或四个相对简单易得的原料出发，不经中间体的分离，直接获得结构复杂的分子的合成方法[1]。多组分反应具有操作简单、分离和纯化步骤少、原子经济性高和环境友好等诸多特点[2] [3]。多组分一锅法作为一类重要的有机化学反应，在新药设计与合成、组合化学、农药研究领域和天然产物合成中有着广泛的应用[4] [5]。

多取代吡喃[2,3-c]吡唑衍生物的研究一直得到广泛的关注，它具有广泛的药理活性，例如抗炎[6]，抗癌[7]，抗菌[8]和镇痛[9]等。

本文以丙酰乙酸甲酯或丙酰乙酸乙酯，苯肼，芳香醛和丙二腈等四组分为反应物，在离子液体[Bmim]BF_4的催化下，在乙醇中用一锅反应生成了 6-氨基-4-芳基-3-乙基-1-苯基-4H-吡喃[2,3-c]吡唑-5-腈**(5a~5j)**。该反应具有反应时间短和产率较高等特点。本文利用 IR，^{1}H NMR 和质谱方法对所得到的产物进行了结构表征。

2. 实验部分

2.1. 仪器与试剂

产物的熔点用瑞士 BUCHIB2540 型熔点仪测定(温度计未校正)；质谱用 API 2000 质谱仪测定；核磁共振用 VARIANINOVA400 型核磁共振仪测定(DMSO-d_6 为溶剂，TMS 为内标)；红外光谱用 BRUKER-EQUINOX55 红外光谱仪测定(KBr 压片)；元素分析用 EA-1110 元素分析仪测定。实验所用选的剂试均为分析纯试剂，除殊特说明外均没经处理直接使用。

2.2. 6-氨基-4-芳基-3-乙基-1-苯基-4-氢吡喃[2,3-c]吡唑-5-腈的合成(5a~5j)

将 2.0 mmol 丙酰乙酸甲酯或丙酰乙酸乙酯和 2.0 mmol 苯肼溶于 2.0 mmol 离子液体[Bmim]BF_4中加热反应 2 分钟，向反应物中依次加入 2.0 mmol 芳香醛，2.0 mmol 丙二腈，继续加热 15~25 分钟。反应完成后，冷却至室温，加入 10 mL 蒸馏水，抽滤，用 EtOH/H_2O 洗涤，然后用 DMF/H_2O 重结晶粗产物得到目标化合物 **5a~5j**。光谱数据如下：

6-*Amino*-4-*phenyl*-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]*pyrazole*-5-*carbonitrile* (5*a*).白色晶体；m.p. 223℃~224℃. IR (KBr, ν/cm^{-1}): 3472, 3319 (NH_2), 2195 (C≡N), 1660, 1592, 1515 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (t, 3H, J = 7.2 Hz, CH_3), 2.12 (q, 2H, J = 7.6 Hz, CH_2), 4.70 (s, 1H, CH), 7.20 (s, 2H, NH_2), 7.25~7.81 (m, 10H, 2Ph-H). MS, m/z (%): 365 ([M+Na]$^+$, 45), 343 ([M+H]$^+$, 100). Anal. Calcd for $C_{21}H_{18}N_4O$ (342.40): C 73.67, H 5.30, N 16.36; found C 73.48, H 5.26, N 16.19.

6-*Amino*-4-(4-*methylphenyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]-*pyrazole*-5-*carbonitrile* (5*b*). m.p. 225℃~226℃. IR (KBr, ν/cm^{-1}): 3468, 3318 (NH_2), 2199(C≡N), 1660, 1592, 1515 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (t, 3H, J = 7.6 Hz, CH_3), 2.14 (q, 2H, J = 7.2 Hz, CH_2), 2.29 (s, 3H, CH_3), 4.65 (s, 1H, CH), 7.14 (s, 2H, NH_2), 7.10~7.16 (dd, 4H, J = 8.0 Hz, p-H_3C-C_6H_4), 7.30 (t, 1H, J = 7.2 Hz, J = 7.6 Hz, Ph-H), 7.48 (t, 2H, J = 7.6 Hz, J = 8.8 Hz, Ph-H), 7.80 (d, 2H, J = 8.8 Hz, Ph-H). MS, m/z (%): 379 ([M+Na]$^+$, 35), 357 ([M+H]$^+$, 100). Anal. Calcd for $C_{22}H_{20}N_4O$ (356.43): C 74.14, H 5.66, N 15.72; found C 74.02, H 5.55, N 15.67.

6-*Amino*-4-(4-*methoxyphenyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]-*pyrazole*-5-*carbonitrile* (5*c*). 白色晶体； m.p. 247℃~248℃. IR (KBr, ν/cm^{-1}): 3399, 3204(NH_2), 2191(C≡N), 1660, 1595, 1513(C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (t, 3H, J = 7.6 Hz, CH_3), 2.15 (q, 2H, J = 7.6 Hz, CH_2), 3.74 (s, 3H, OCH_3), 4.65 (s, 1H, CH), 6.88 (d, 2H, J = 8.8 Hz, p-H_3CO-C_6H_4), 7.15 (s, 2H, NH_2), 7.16 (d, 2H, J = 8.8 Hz, p-H_3CO-C_6H_4), 7.32 (t, 1H, J = 7.2 Hz, J = 7.6 Hz, Ph-H), 7.48 (t, 2H, J = 7.6 Hz, Ph-H), 7.80 (d, 2H, J = 7.6 Hz, Ph-H). MS, m/z (%): 395 ([M+Na]$^+$, 100), 373 ([M+H]$^+$, 90). Anal. Calcd for $C_{22}H_{20}N_4O_2$ (372.43): C, 70.95; H, 5.41; N, 15.04; found C 70.82, H 5.38, N 14.94.

6-*Amino*-4-(4-*chlorophenyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]-*pyrazole*-5-*carbonitrile* (5*d*). 白色晶体；m.p. 232℃~235℃. IR (KBr, ν/cm^{-1}): 3452, 3323 (NH_2), 2198 (C≡N), 1660, 1594, 1517 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, 3H, J = 8Hz, CH_3), 2.15 (q, 2H, J = 7.2 Hz, CH_2), 4.75 (s, 1H, CH), 7.25 (s, 2H, NH_2), 7.30 (d, 2H, J = 8.4Hz, p-Cl-C_6H_4), 7.32 (t, J = 8.4 Hz, J = 7.6 Hz, 1H, Ph-H), 7.40 (d, 2H, J = 8.4 Hz, p-Cl-C_6H_4), 7.50 (t, J = 8.4 Hz, 2H, Ph-H), 7.80 (d, J = 7.6 Hz, 2H, Ph-H). MS, m/z (%): 400 ([M+1+Na]$^+$, 8), 399 ([M+Na]$^+$, 20), 378 ([M+1+H]$^+$, 30), 377 ([M+H]$^+$, 100). Anal. Calcd for $C_{21}H_{17}ClN_4O$ (376.85): C 66.93, H 4.55, N 14.87; found C 66.82, H 4.52, N 14.74.

6-*Amino*-4-(4-*bromophenyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]-*pyrazole*-5-*carbonitrile* (5*e*). 白色晶体； m.p. 243℃~245℃; IR (KBr, ν/cm^{-1}): 3448, 3324 (NH_2), 2195 (C≡N), 1659, 1596, 1518 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, 3H, J = 7.2 Hz, CH_3), 2.15 (q, 2H, J = 7.6 Hz, CH_2), 4.74 (s, 1H, CH), 7.24 (d, 2H, J = 8.4 Hz, p-Br-C_6H_4), 7.25 (s, 2H, NH_2), 7.33 (t, 1H, J = 7.2 Hz, J = 7.6 Hz, Ph-H), 7.49 (t, 2H, J = 7.6 Hz, J = 8.4 Hz, Ph-H), 7.53 (d, 2H, J = 8.4 Hz, p-Br-C_6H_4), 7.80 (d, 2H, J = 8.4 Hz, Ph-H). MS, m/z (%): 445 ([M+2+Na]$^+$, 35), 443 ([M+Na]$^+$, 30), 423 ([M+2+H]$^+$, 98), 421 ([M+H]$^+$, 100). Anal. Calcd for $C_{22}H_{19}BrN_4O$ (421.30): C 59.87, H 4.07, N 13.30; found C 59.68, H 4.04, N 13.14.

6-*Amino*-4-(4-*floroyphenyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]-*pyrazole*-5-*carbonitrile* (5*f*). 白色晶体；m.p. 233℃~234℃. IR (KBr, ν/cm^{-1}): 3456, 3325 (NH_2), 2200 (C≡N), 1665, 1596, 1515 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.87 (t, 3H, J = 7.6 Hz, CH_3), 2.13 (q, 2H, J = 7.6 Hz, CH_2), 4.74 (s, 1H, CH), 7.15 (d, 2 H, J = 8.8 Hz, p-F-C_6H_4), 7.21 (s, 2H, NH_2), 7.30 (t, 1H, J = 7.6 Hz, Ph-H), 7.50 (t, 2H, J = 7.6 Hz, J = 8.4 Hz, Ph-H), 7.32 (d, 2H, J = 8.8 Hz, p-F-C_6H_4), 7.80 (d, 2H, J = 8.8 Hz, J = 8.0 Hz, Ph-H). MS, m/z (%): 384 ([M+Na]$^+$, 10), 383 ([M+Na]$^+$, 25), 362 ([M+1+H]$^+$, 58), 361 ([M+H]$^+$, 100). Anal. Calcd for $C_{21}H_{17}FN_4O$ (360.39): C 69.99, H 4.75, N 15.55; found: C 69.72, H 4.72, N 15.44.

6-*Amino*-4-(4-*nitrophenyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]-*pyrazole*-5-*carbonitrile* (5*g*). 土黄色晶体； m.p. 221℃~222℃. IR (KBr, ν/cm^{-1}): 3435, 3328 (NH_2), 2205 (C≡N), 1666, 1591, 1517 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.89 (t, 3H, J = 7.6 Hz, CH_3), 2.14 (q, 2H, J = 7.2 Hz, CH_2), 4.95 (s, 1H, CH), 7.32 (t, 1H, J = 7.2 Hz, Ph-H), 7.37 (s, 2H, NH_2), 7.49 (t, 2H, J = 7.6 Hz, J = 8.4 Hz, Ph-H), 7.58 (d, 2H, J = 8.8 Hz, p-O_2N-C_6H_4), 7.81 (d, 2H, J = 8.8 Hz, Ph-H), 8.22 (d, 2H, J = 8.8 Hz, p-O_2N-C_6H_4). MS, m/z (%):410 ([M+Na]$^+$, 40), 388 ([M+H]$^+$, 100). Anal. Calcd for $C_{21}H_{17}N_5O_3$ (387.40): C 65.11, H 4.42, N 18.08;

found C 65.02, H 4.32, N 17.94.

6-*Amino*-4-(4-*hydroxyphenyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]-*pyrazole*-5-*carbonitrile* (5*h*). 白色晶体； m.p. 227℃~229℃. IR (KBr, ν/cm^{-1}): 3396 (OH), 3320, 3202 (NH_2), 2177 (C≡N), 1657, 1579, 1516 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (t, 3H, J = 7.6 Hz, CH_3), 2.14 (q, 2H, J = 7.6 Hz, CH_2), 4.58 (s, 1H, CH), 6.70 (d, 2H, J = 8.4 Hz, p-HO-C_6H_4), 7.03 (d, 2H, J = 8.4 Hz, p-HO-C_6H_4), 7.11 (s, 2H, NH_2), 7.32 (t, 1H, J = 7.2 Hz, J = 7.6 Hz, Ph-H), 7.49 (t, 2H, J = 8.4 Hz, J = 7.6 Hz, Ph-H), 7.78 (d, 2H, J = 7.6 Hz, Ph-H), 9.33 (s, 1H, OH). MS, m/z (%): 381 ([M+Na]$^+$, 40), 359 ([M+H]$^+$, 100). Anal. Calcd for $C_{21}H_{18}N_4O_2$ (358.40): C 70.38, H 5.06, N 15.63; found C 70.22, H 4.99, N 15.54.

6-*Amino*-4-(3-*pyridyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]*pyrazole*-5-*carbonitrile* (5*i*). 白色晶体；m.p. 249℃~251℃. IR (KBr, ν/cm^{-1}): 3362, 3090 (NH_2), 2189 (C≡N), 1661, 1585, 1517 (C=N, C=C). ^{1}HNMR (400 MHz, DMSO-d_6) δ: 0.87 (t, 3H, J = 7.6 Hz, CH_3), 2.14 (q, 2H, J = 7.6 Hz, CH_2), 4.81 (s, 1H, CH), 7.30 (s, 2H, NH_2), 7.31(t, 1H, J = 7.6 Hz, J = 8.4 Hz, Ph-H), 7.38 (m. 2 H, J = 4.8 Hz, J = 7.6 Hz, pyridyl-H), 7.50 (t, 2H, J = 8.4 Hz, Ph-H), 7.66 (d. 1H, J = 2.4 Hz, J = 1.6 Hz, J = 8.4 Hz, pyridyl-H), 7.80 (d, 2H, J = 8.0 Hz, Ph-H), 8.50 (d, 1H, J = 1.6 Hz, J = 2.4 Hz, J = 5.2 Hz, pyridyl-H), 8.55 (d, 1H, J = 2.4 Hz, pyridyl-H). MS, m/z (%): 366 ([M+Na]$^+$, 55), 344 ([M+H]$^+$, 100). Anal.Calcd for $C_{20}H_{17}N_5O$ (343.39): C 69.96, H 4.99, N 20.39; found C 69.82, H 4.90, N 20.22.

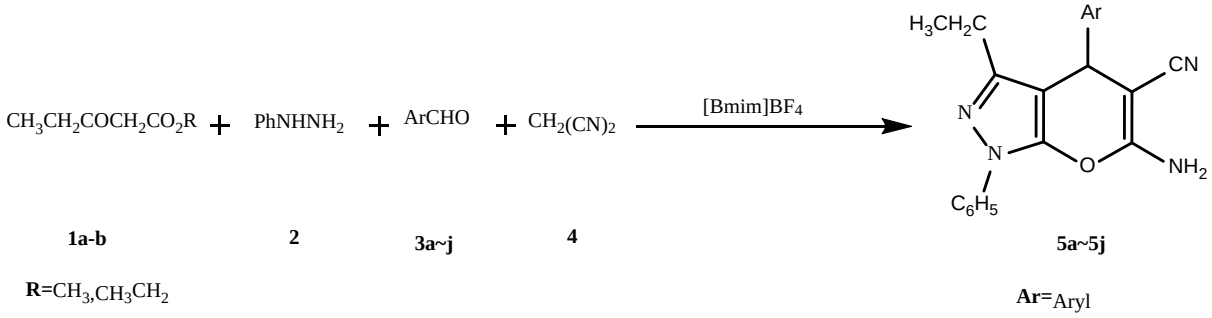
6-*Amino*-4-(1-*naphtyl*)-1,4-*dihydro*-3-*ethyl*-1-*phenyl* *pyrano*[2,3-*c*]*pyrazole*-5-*carbonitrile* (5*j*).白色晶体；m.p. 189℃~190℃. IR (KBr, ν/cm^{-1}): 3375, 3176 (NH_2), 2185 (C≡N), 1658, 1591, 1515 (C=N, C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.65 (t, 3H, J = 7.6Hz, CH_3), 1.91 (q, 2H, J = 7.6 Hz, CH_2), 4.35 (s, 1H, CH), 7.22 (s, 2H, NH_2), 7.32−7.99 (m, 12H, Ar-H). MS, m/z (%): 415 ([M+H]$^+$, 100), 393 ([M+Na]$^+$, 50). Anal. Calcd for $C_{25}H_{20}N_4O$ (392.46): C 76.51, H 5.14, N 14.28; found C 76.40, H 5.10, N 14.17.

目标化合物 **5a~5j** 用 ^{1}H NMR 进行结构表征，在 δ 4.35~4.95 呈现的单峰为吡喃环 4 位上的 CH 质子信号，在 δ7.11~7.37 范围内呈现的单峰为 NH_2 中的质子信号。

3. 结果与讨论

该反应在离子液体[Bmim]BF_4 催化下，以丙酰乙酸甲酯或丙酰乙酸乙酯，苯肼，芳香醛和丙二腈原料，经过一锅法以较高的产率合成了以下 10 种目标化合物(**5a~5j**)。该反应具有时间短(7~15 min)，产率较高，操作简便等特点(图 1)。

从实验结果可以总结出(表 1)，芳环上取代基的对该反应速度有一定的影响，当苯环对位有吸电子基团时，反应速度比有供电子基团的化合物要快，这可能是因为吸电子基团有利于亲核加成反应的进行有关。



Scheme 1. Synthesis of 6-amino-4-aryl-1,4-dihydro-3-ethyl-1-phenyl pyrano[2,3-*c*]-pyrazole-5-carbonitrile (5a~5j)
图 1. 6-氨基-4-芳基-3-乙基-1-苯基-4-氢吡喃[2,3-c]吡唑-5-腈的合成(5a~5j)

Table 1. The reaction times and yields of compounds 5a~5j
表 1. 化合物 5a~5j 的反应时间和产率

Entry	Ar	Product	Time (min)	Yields (%) R = CH_3/CH_3CH_2
1	C_6H_5	**5a**	12	75/60
2	*p*-$H_3CC_6H_4$	**5b**	10	78/71
3	*p*-$H_3COC_6H_4$	**5c**	10	93/80
4	*p*-ClC_6H_4	**5d**	8	86/74
5	*p*-BrC_6H_4	**5e**	8	94/85
6	*p*-FC_6H_4	**5f**	7	83/70
7	*p*-$O_2NC_6H_4$	**5g**	8	65/58
8	*p*-HOC_6H_4	**5h**	8	90/82
9	3-Pyridyl	**5i**	8	88/82
10	1-Naphtyl	**5j**	15	71/60

[a]Isolated yields.

4. 结论

在离子液体[Bmim]BF_4 催化下以丙酰乙酸甲酯或丙酰乙酸乙酯，苯肼，芳醛和丙二腈等四组分为原料经过一锅法合成了一系列多取代吡喃[2,3-c]吡唑类化合物。该方法具有时间短，产率较高，操作简便等特点。

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