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Synthesis of 3,4-Dihydropyrimidine-2-(1*H*)-Ones/Thiones Catalyzed by Ionic Liquid [C_2O_2BBTA][TFA]

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Abstract

Carboxyl functional ionic liquid with benzotriazole cation and trifluoroacetate anion can be used as environmental-friendly catalyst for the efficient synthesis of 3,4-dihydropyrimidin-2(1*H*) ones /thiones under solvent-free conditions. Moreover, the ionic liquid [C_2O_2BBTA][TFA] can be easily recycled and reused for at least four cycles without obvious loss of catalytic activity.

Keywords

Ionic Liquids, Catalysis, Solvent-Free, 3,4-Dihydropyrimidin-2(1*H*)-Ones/Thiones

离子液体[C_2O_2BBTA][TFA]催化合成3,4-二氢嘧啶-2-(1*H*)-酮/硫酮

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摘　要

无溶剂条件下，阳离子为苯并三唑、阴离子为三氟乙酸根的羧基功能化离子液体作为环境友好的催化剂，

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高效地合成了一系列3,4-二氢嘧啶-2(1*H*)-酮或硫酮。此外，离子液体[C_2O_2BBTA][TFA]循环使用至少4次，且催化活性没有明显降低。

关键词

离子液体，催化，无溶剂，3,4-二氢嘧啶酮-2(1*H*)-酮/硫酮

1. 引言

众所周知，3,4-二氢嘧啶-2(1*H*)-酮/硫酮化合物具有抗过敏、降压、杀菌、消炎、抗病毒[1]-[6]及抑制有丝分裂驱动蛋白[7] [8]等重要的药理和生物活性。100 多年前，意大利化学家 Biginelli 首次提出了浓盐酸催化苯甲醛、尿素和乙酰乙酸乙酯三组分反应合成 3,4-二氢嘧啶-2(1*H*)-酮/硫酮的方法[9]。然而该方法存在条件苛刻、反应时间长(18 h)且产率低(20%~50%)的缺点。因此，各种催化体系被用于该反应以改进经典方法的不足，如多组分聚合物 1,4-DHP 和 3,4-DHPM [10]、纳米共催化剂 TiO_2-SiO_2 [11]、Cu-EDTA 负载的 APTMS-Fe_3O_4@SiO_2 核-壳体系[12]、硅钛铝氧化物 MxOy [13]、微波促进[14]等。

离子液体因具有蒸气压低、热稳定性好、毒性低、易于回收等诸多优点，在 Biginelli 反应中也得到了应用[15] [16]。基于本课题组在离子液体合成和催化应用领域的研究基础[17] [18]，本文提出了一种 Brønsted 酸性苯并三唑离子液体催化合成 3,4-二氢嘧啶-2(1*H*)-酮/硫酮的方法。考察了催化剂种类和用量、反应溶剂、反应时间等因素对反应产率的影响，同时对反应底物的普适性进行了研究。此外，还探讨了离子液体的催化循环使用效果。

2. 实验部分

2.1. 试剂与仪器

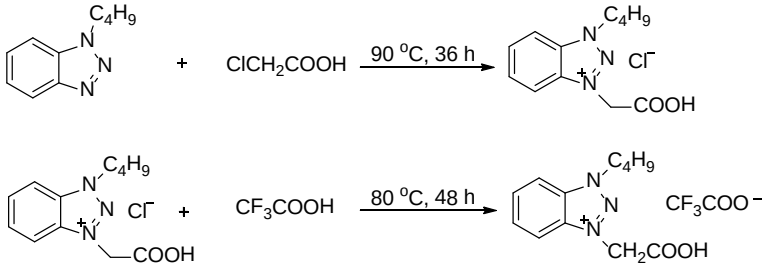
薄层层析硅胶用 GF254 硅胶，柱层析硅胶：300-400 目(青岛海洋化工厂)。美国 Varian inova-400 型核磁共振仪(400 MHz, TMS)；德国 Bruker Equinox 55 红外光谱仪(KBr 压片)；美国 HP 1100 液相色谱质谱仪；瑞士 Büchi B-560 型熔点仪。所用试剂均为市售分析纯，用前未经处理。

2.2. 离子液体的合成

离子液体 1-丁基-3-羧甲基苯并三唑三氟乙酸盐的合成如式 1 所示。将 0.20 mol 的 1-丁基苯并三唑和 0.24 mol 的 1-氯乙酸在 90℃搅拌反应 36 h，冷却至室温，用乙醚和丙酮(V:V = 2:1, 3 × 20 mL)混合溶剂浸泡洗涤所得的棕色固体，抽滤，所得固体在 90℃下真空干燥 10 h，即得氯化 1-丁基-3-羧甲基苯并三唑[19]，白色固体，熔点：148℃~149℃。

在室温下，将 0.012 mol 三氟乙酸缓慢滴加到 0.01 mol 氯化 1-丁基-3-羧甲基苯并三唑中，滴毕升温至 80℃回流反应 48 h，得到褐色液体，减压旋除过量的三氟乙酸，残余物在 90℃下真空干燥 10 h，即得离子液体 1-丁基-3-羧甲基苯并三唑三氟乙酸盐[C_2O_2BBTA][TFA]。

离子液体[C_2O_2BBTA][TFA]表征数据：褐色液体，[C_2O_2BBTA][TFA]：^{1}H NMR (400 MHz, DMSO) δ: 8.79-8.24 (m, 3H), 8.06-7.96 (m, 2H), 5.93 (s, 2H), 5.08 (t, *J* = 7.1 Hz, 2H), 2.06-1.99 (m, 2H), 1.39-1.31 (m,



Scheme 1. The synthesis of ionic liquid [C_2O_2BBTA][TFA]
图式 1. 离子液体[C_2O_2BBTA][TFA]的合成

2H), 0.93 (t, *J* = 7.4 Hz, 3H), ^{13}C NMR (100 MHz, DMSO) δ: 166.26 134.99, 134.22, 131.13, 130.80, 120.96, 117.76, 114.22, 113.85, 52.66, 51.09, 30.27, 18.81, 13.09. IR (KBr, ν/cm-1): 3106, 2967, 2940, 2879, 2511, 1738, 1505, 1471, 1364, 1190, 1141, 1029, 754, 718, 643, 599. ESI-MS: m/z (%) = 234.1 (100%) [M + H] $^+$.

2.3. 未知化合物 4a-4s 的合成及结构分析

化合物 **4a-4r** 的合成反应如图式 2 所示。在 10 mL 圆底烧瓶中加入 2 mmol 芳香醛、2 mmol *β*-二羰基化合物和 3 mmol 脲或硫脲，20 mol%催化剂[C_2O_2BBTA][TFA]，混合均匀后在 90℃无溶剂条件下磁力搅拌反应 40 min。反应结束后，向混合物中加入大量的碎冰，室温充分搅拌至碎冰融化，过滤即得产物粗品，经过柱层析分离得化合物 **4a-4r** 纯品。化合物结构经 ^{1}H NMR，^{13}C NMR，IR 和 MS 确证结构。

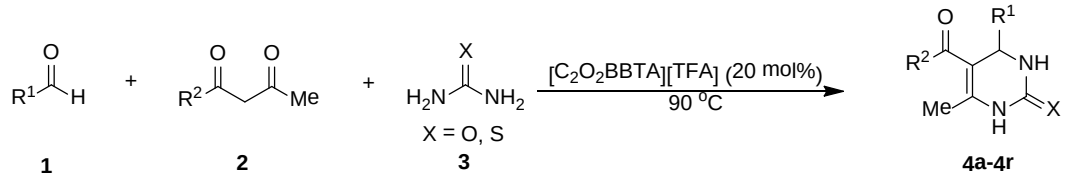
目标化合物的表征如下：

4g： 白色固体；^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.30 (s, 1H), 7.74 (s, 1H), 7.36 (ddd, *J* = 15.0, 8.8, 4.4 Hz, 2H), 7.21 (d, *J* = 2.5 Hz, 1H), 5.60 (d, *J* = 2.8 Hz, 1H), 3.90 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.76, 162.01, 159,55, 151.10, 149.30, 138.29, 138.26, 132.28, 130.27, 130.17, 116.34, 116.09, 114.97, 97.63, 58.99, 50.91, 40.02, 17.56, 13.81; IR (KBr, ν/cm^{-1}): 3346, 3225, 3112, 2976, 1697, 1644, 1223, 1093, 903, 805; ESI-MS: m/z (%) = 335.0 (100%) [M +Na] $^+$.

4h：白色固体；^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.32 (s, 1H), 7.78 (s, 1H), 7.48 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.23 – 6.92 (m, 2H), 5.59 (s, 1H), 3.91 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 164.71, 162.18, 159.75, 151.00, 149.73, 143.89, 143.83, 131.17, 131.09, 126.86, 116.28, 115.27, 115.03, 97.11, 59.04, 51.76, 17.60, 13.78; IR (KBr, ν/cm^{-1}): 3221, 3098, 2982, 1703, 1650, 1604, 1282, 1237, 1103, 881, 803; ESI-MS: m/z (%) = 335.0 (100%) [M + Na] $^+$.

4i： 白色固体；^{1}H NMR (400 MHz, DMSO) δ: 9.30 (s, 1H), 7.79 (s, 1H), 7.49 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.35 (t, *J* = 8.7 Hz, 1H), 7.27 (dd, *J* = 4.9, 2.2 Hz, 1H), 5.15 (d, *J* = 3.3 Hz, 1H), 4.18 – 3.86 (m, 2H), 2.26 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 165.00, 158.49, 156.06, 151.66, 148.95, 142.90, 142.87, 131.19, 127.48, 127.40, 116.86, 116.64, 107.63, 107.42, 98.42, 59.21, 52.97, 17.72, 13.93, IR (KBr, ν/cm^{-1}): 3342, 3203, 3100, 2984, 1702, 1658, 1232, 1099, 895, 804; ESI-MS: m/z (%) = 379.0 (100%) [M + Na] $^+$.

4m： 白色固体；^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.15 (s, 1H), 7.70 (s, 1H), 7.24 (t, H), 6.76-6.83 (m, 3H), 5.10 (s, 1H), 4.82 (m, 1H), 3.72 (s, 3H), 2.23 (s, 3H), 1.16 (d, *J* = 8.0 Hz, 3H), 1.01 (d, *J* = 8.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 164.73, 159.07, 152.07, 148.05, 146.35, 129.37, 118.20, 112.33, 112.00, 99.34, 66.25, 54.86, 53.73, 21.69, 21.40, 17.60, IR (KBr, ν/cm^{-1}): 3234, 3106, 2981, 2948, 1721, 1652, 1599, 1463, 1431, 1374, 1282, 1232, 1092, 1073, 788; ESI-MS: m/z (%) = 327.1 (100%) [M + Na] $^+$.



Scheme 2. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (4a-4r)
图式 2. 3,4-二氢嘧啶酮/硫酮(4a-4r)的合成

4n：橙色固体；^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.32 (s, 1H), 9.07 (s, 1H), 7.59 (s, 1H), 7.02 (d, *J* = 4.0 Hz, 2H), 6.68 (d, *J* = 4.0 Hz, 2H), 5.02 (s, 1H), 4.82-4.78 (m, 1H), 2.22 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 164.79, 156.39, 152.03, 147.35, 135.47, 127.35, 114.80, 99.92, 66.10, 53.44, 21.69, 21.39, 17.56; IR (KBr, ν/cm^{-1}): 3289, 3227, 3109, 2979, 2808, 1706, 1686, 1651, 1511, 1448, 1371, 1282, 1226, 1173, 1086, 783, 680; ESI-MS: m/z (%) = 313.1 (100%) [M + Na]$^{+}$.

4o：绿色固体；^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.05 (s, 1H), 7.56 (s, 1H), 7.03 (d, *J* = 4.0 Hz, 2H), 6.65 (d, *J* = 4.0 Hz, 2H), 5.01 (s, 1H), 4.82-4.80 (m, 1H), 2.84 (s, 6H), 2.22(s, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 164.87, 152.17, 149.62, 147.15, 132.80, 126.80, 112.04, 100.12, 66.08, 53.25, 21.72, 21.47, 17.56; IR (KBr, ν/cm^{-1}): 3243, 3116, 2980, 2937, 1719, 1648, 1526, 1457, 1363, 1290, 1231, 1090, 789; ESI-MS: m/z (%) = 340.1 (100%) [M + Na]$^{+}$.

4p：淡黄色固体；^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.10 (s, 1H), 7.67 (s, 1H), 7.22-7.26 (m, 2H), 7.13-7.14 (m, 2H), 5.08 (s, 1H), 2.21 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 164.61, 162.38, 159.97, 151.81, 147.44, 141.16, 141.13, 128.20, 128.13, 115.03, 114.82, 100.25, 79.10, 53.60, 27.72, 17.56; IR (KBr, ν/cm^{-1}): 3230, 3107, 2975, 2930, 1697, 1644, 1507, 1452, 1366, 1292, 1230, 1164, 1090, 1035, 837, 798, 759, 658; ESI-MS: m/z (%) = 329.1 (100%) [M + Na]$^{+}$.

4q：淡黄色固体；^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.05 (d, *J* = 1.6 Hz, 1H), 7.64 – 7.63 (m, 1H), 7.23-7.21 (m, 1H), 7.06 – 7.02 (m, 3H), 5.07 (d, *J* = 3.2 Hz, 1H), 2.28 (s, 3H), 2.21 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 164.73, 152.06, 147.05, 144.89, 137.07, 128.13, 127.68, 126.80, 123.23, 100.50, 78.99, 54.20, 27.73, 21.01, 17.56; IR (KBr, ν/cm^{-1}): 3226, 3099, 2977, 2935, 1699, 1647, 1489, 1438, 1366, 1294, 1232, 1165, 1087, 859, 813, 774, 745, 697,670,599; ESI-MS: m/z (%) = 325.1 (100%) [M + Na]$^{+}$.

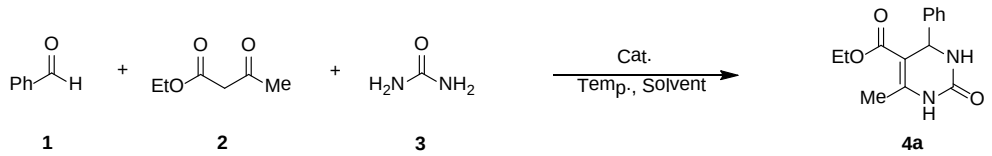
4r：淡黄色固体；^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.08 (s, 1H,); 7.68 – 7.67 (m, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 6.83 – 6.78 (m, 3H), 5.08 (d, *J* = 3.2 Hz, 1H), 3.73 (s, 3H), 2.22 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 164.74, 159.07, 152.14, 147.29, 146.36, 129.35, 118.14, 112.26, 111.98, 100.35, 79.05, 54.85, 53.95, 27.74, 17.57; IR (KBr, ν/cm^{-1}): 3392, 3247, 3111, 2972, 2937, 1707, 1672, 1519, 1463, 1366, 1282, 1240, 1165, 1094, 1038, 849, 801; ESI-MS: m/z (%) = 341.1 (100%) [M + Na]$^{+}$.

3. 结果与讨论

3.1. 最优反应条件的筛选

以苯甲醛、乙酰乙酸乙酯和脲三组分反应为模型，考察了催化剂种类和用量、溶剂种类、反应时间等因素对反应的影响。首先考察了 2 种不同阴离子的 1-丁基-3-羧甲基苯并三唑离子液体及相应 Brønsted 酸三氟乙酸对反应的影响(表 1, entries 1-3)。从表中可以看出，离子液体[C_2O_2BBTA][TFA]的催化活性优于离子液体[C_2O_2BBTA]Cl 和三氟乙酸。其次，考察了催化剂的用量对反应体系的影响(表 1, entries 4, 5)，发现催化剂用量为 20 mol%时，产物产率最高为 96%。随后考察了 H_2O、CH_3OH、C_2H_5OH、*i*-PrOH、

Table 1. Optimization of reaction conditions[a]
表 1. 反应条件的优化 [a]



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

Entry	Catalyst	Solvent	Time	Yield (%)[b]
1	[C_2O_2BBTA]Cl (20% mol)	-	40 min	85
2	**[C_2O_2BBTA][TFA] (20% mol)**	**-**	**40 min**	**96**
3	CF_3COOH (20% mol)	-	40 min	96
4	[C_2O_2BBTA][TFA] (10% mol)	-	40 min	85
5	[C_2O_2BBTA][TFA] (30% mol)	-	40 min	95
6	[C_2O_2BBTA][TFA] (20% mol)	H_2O	40 min	5
7	[C_2O_2BBTA][TFA] (20% mol)	MeOH	40 min	6
8	[C_2O_2BBTA][TFA] (20% mol)	EtOH	40 min	10
9	[C_2O_2BBTA][TFA] (20% mol)	*i*-PrOH	40 min	48
10	[C_2O_2BBTA][TFA] (20% mol)	CH_2Cl_2	40 min	16
11	[C_2O_2BBTA][TFA] (20% mol)	CH_3CN	40 min	19
12	[C_2O_2BBTA][TFA] (20% mol)	DMF	40 min	0
13	[C_2O_2BBTA][TFA] (20% mol)	Toluene	40 min	5
14	[C_2O_2BBTA][TFA] (20% mol)	-	50 min	91
15	[C_2O_2BBTA][TFA] (20% mol)	-	60 min	93
16	[C_2O_2BBTA][TFA] (20% mol)	-	30 min	94
17	[C_2O_2BBTA][TFA] (20% mol)	-	20 min	91

[a]反应条件：苯甲醛(2 mmol)，乙酰乙酸乙酯(2 mmol)，脲(3 mmol) %，90℃；[b]分离产率。

CH_2Cl_2、CH_3CN、DMF、甲苯等八种溶剂及无溶剂条件下反应的效果，发现无溶剂条件下反应效果最佳(表 1, entries 6-13)。最后我们对反应时间进行了筛选(表 1, entries 14-17)，结果表明最佳反应时间是 40 min。因此，最优的反应条件为：无溶剂条件下，离子液体[C_2O_2BBTA][TFA](20 mol%)为催化剂，90℃反应 40 min。

3.2. 底物普适性研究

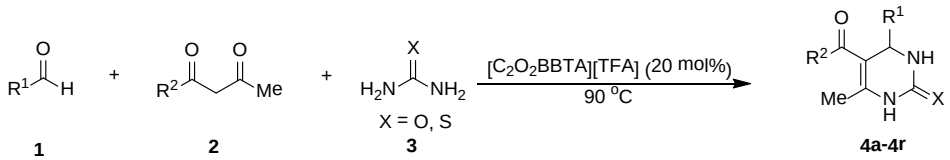
在最优条件下，我们对该反应的底物普适性进行了研究，结果见表 2。从中可以看出，苯甲醛的苯环上不管是带有供电子基团还是吸电子基团，都能顺利的参与反应，以 82%~98%的收率得到相应的 3,4-二氢嘧啶-2(1*H*)-酮产物(表 2**,** entries **4a-4j**)。硫脲代替脲也被用于 Biginelli 三组分反应，成功地合成了相应的产物(表 2, entries **4k, 4l**)。使用乙酰乙酸异丙酯、乙酰乙酸叔丁酯代替 1,3-二羰基化合物参与反应也能得到令人满意的结果，相应产物的产率为 89%~99% (表 2**,** entries **4m-4r**)。因此，离子液体 1-丁基-3-羧甲基苯并三唑三氟乙酸盐催化合成二氢嘧啶-2(1*H*)-酮/硫酮化合物具有很好的底物普适性。

3.3. 离子液体循环使用性

离子液体的特性之一是循环使用，本文以苯甲醛、乙酰乙酸乙酯和脲三组分反应为模型，在最优条件下考察了离子液体催化剂 1-丁基-3-羧甲基苯并三唑三氟乙酸盐的循环使用效果。具体方法为：将反应

结束萃取分离的水相减压旋除水，残余物经真空干燥至恒重，即得回收的离子液体[C_2O_2BBTA][TFA]，可直接用于下一次催化循环。从图 1 可知，离子液体催化剂 1-丁基-3-羧甲基苯并三唑三氟乙酸盐循环使用 4 次后仍能保持较好的催化活性，表明该离子液体具有较好的循环使用效果。

Table 2. Investigation of substrate scope[a]
表 2. 底物普适性研究 [a]



1 2 3 4a-4r

Entry	R^1	R^2	X	Yields[b] (%)	Mp (℃)[c]	
					Found	Reported (lit.)
4a	C_6H_5	EtO	O	96	201-202	200-202 [20]
4b	4-Me-C_6H_4	EtO	O	97	209-211	209-212 [21]
4c	3-MeO-C_6H_4	EtO	O	93	219-221	219-220 [20]
4d	4-F-C_6H_4	EtO	O	98	175-176	175-177 [22]
4e	2-Cl-C_6H_4	EtO	O	93	211-213	211-213 [23]
4f	2-Br-C_6H_4	EtO	O	93	202-204	205-207 [24]
4g	2-Cl-4-F-C_6H_3	EtO	O	88	195-197	
4h	2-Cl-5-F-C_6H_3	EtO	O	82	219-221	
4i	3-Br-4-F-C_6H_3	EtO	O	85	193-195	
4j	3,4-$(HO)_2$-C_6H_3	EtO	O	89	232-234	233-235 [20]
4k	C_6H_5	EtO	S	83	201-204	202-204 [25]
4l	4-Me-C_6H_4	EtO	S	90	184-186	185-186 [26]
4m	3-MeO-C_6H_4	*i*-PrO	O	94	196-198	
4n	4-HO-C_6H_4	*i*-PrO	O	98	192-194	
4o	4-$N(CH_3)_2$-C_6H_4	*i*-PrO	O	89	260-263	
4p	4-F-C_6H_4	*t*-BuO	O	99	147-149	
4q	3-Me-C_6H_4	*t*-BuO	O	93	217-219	
4r	3-MeO-C_6H_4	*t*-BuO	O	95	212-214	

[a] 反应条件：芳香醛(2 mmol)，1,3-二羰基化合物(2 mmol)，脲或硫脲(3 mmol)，[C_2O_2BBTA][TFA] (20 mol%)，90℃，40 min；[b] 分离产率。

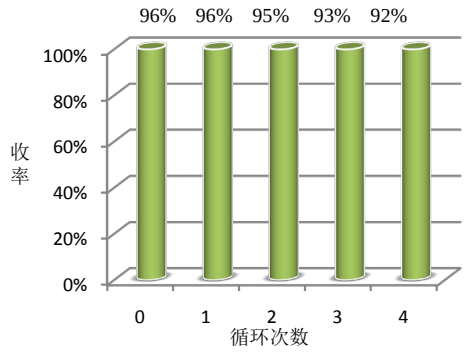


Figure 1. Recycling research of ionic liquid [C_2O_2BBTA][TFA]
图 1. 离子液体[C_2O_2BBTA][TFA]的循环使用研究

4. 结论

本文发展了一种离子液体 1-丁基-3-羧甲基苯并三唑三氟乙酸盐催化芳香醛、1,3-二羰基化合物和脲或硫脲绿色、高效合成 3,4-二氢嘧啶-2(1*H*)-酮或硫酮的方法。该方法具有对环境友好、反应时间短、产率高等优点，离子液体催化剂可循环使用 4 次并且活性没有明显降低。

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