精细化工中间体

一锅法合成 5-取代异噁唑-3-羧酸甲酯类化合物

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摘要：以甲醇钠为碱催化剂，取代甲基酮与草酸二甲酯经 Claisen 缩合反应合成了 *β*-二羰基化合物，再经浓硫酸中和后与盐酸羟胺反应成肟，最后高温成环，合成了不同取代基的 5-取代异噁唑-3-羧酸甲酯类化合物。通过 ^{1}HNMR、^{13}CNMR、MS 确证了产物结构，对合成过程中的碱催化剂、溶剂、酸中和的条件进行了优化，对不同取代基的 5-取代异噁唑-3-羧酸甲酯化合物合成工艺差异进行了探讨。结果表明，用一锅法成功合成了 26 个 5-取代异噁唑-3-羧酸甲酯。其中，23 个可在单一溶剂甲醇中制备，避免了中间产物的分离和纯化处理，操作流程简捷，单一溶剂易于回收处理；5-叔丁基异噁唑-3-羧酸甲酯（Ⅳc）、5-(4-氨基苯基)异噁唑-3-羧酸甲酯（Ⅳm）和 5-(3-氨基苯基)异噁唑-3-羧酸甲酯（Ⅳn）的合成需要用叔丁醇钾作碱催化剂，并在四氢呋喃中进行；5-三氟甲基异噁唑-3-羧酸甲酯（Ⅳv）的合成未成功，需要设计新的合成方法和条件。

关键词：一锅法；异噁唑-3-羧酸酯；异噁唑；合成；羧酸；精细化工中间体

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One pot synthesis of 5-substituted isoxazole-3-carboxylic acid methyl ester series compounds

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Abstract: A series of 5-substituted isoxazol-3-carboxylate methyl esters with different substituents were synthesized from *β*-dicarbonyl compounds, which were prepared firstly from Claisen condensation reaction of substituted methyl ketones and dimethyl oxalate using sodium methanol as base catalyst, then neutralized by concentrated sulfuric acid, reacted with hydroxylamine hydrochloride to obtain oximes, and finally formed a ring at high temperature. The structure of the products was confirmed by ^{1}HNMR, ^{13}CNMR and MS, while the reaction conditions of alkali catalyst, solvent and acid neutralization in the synthesis process were optimized, with the differences among synthesis processes of 5-substituted isoxazol-3-methyl carboxylate compounds with different substituents discussed. The results showed that 26 5-substituted isoxazol-3- carboxylate methyl esters were successfully synthesized by one-pot method, of which 23 could be prepared in a single solvent methanol. Without separation and purification of intermediate products, it was simple and carried out only in a single solvent, which could be easily recovered. Among the products, 5-*tert*-butylisooxazol-3-carboxylate methyl ester (Ⅳc), 5-(4-aminophenyl)isooxazol-3-carboxylate methyl ester (Ⅳm) and 5-(3-aminophenyl)isooxazol-3-carboxylate methyl ester (Ⅳn) required potassium *tert*-butoxide as base catalyst and tetrahydrofuran as solvent for synthesis, while the synthesis of 5-trifluoromethylisooxazol-3-carboxylate methyl ester (Ⅳv) was unsuccessful, and further development of synthesis technology and optimization conditions were needed.

Key words: one-pot method; isoxazole-3-carboxylates; isoxazole; synthesis; carboxylic acids; fine chemical intermediates

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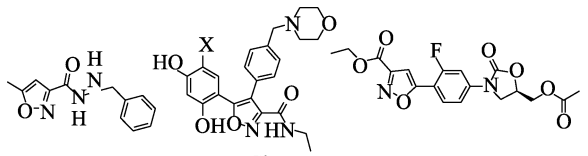
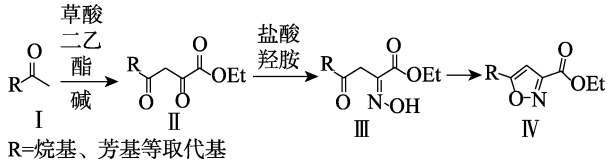
5-取代异噁唑-3-羧酸酯类化合物是重要的精细化工中间体，其分子结构具有一定的药理活性[1-2]，在药物分子设计中，其常被用作生物电子等排体进行药物活性研究[3]。5-甲基异噁唑酰肼（**1**，如下所示）已作为一元胺氧化酶抑制剂用于抗抑郁药物的研究[4]。CALI 等[5]和 TALDONE 等[6]报道了许多含有异噁唑骨架的生物活性分子，如杀虫剂噁菌灵、除草剂异噁唑草酮[7-8]、高效抑菌药新诺明[9]、抗类风湿性关节炎药来氟米特[10]等。2007 年，HAUCK 等[11]研究发现，5-取代苯基异噁唑-3-酰胺类衍生物（**2**）的生物活性和万古霉素相当。2008 年，BROUGH 等[12]研究发现，异噁唑-3-羧酸酯类衍生物（**3**）具有抗癌活性。



1　　**2** X=Cl、Br、I　　**3**

随着更多有效的异噁唑类药物分子的发现，未来市场对 5-取代异噁唑-3-羧酸酯类化合物的需求将逐渐增多，因此，5-取代异噁唑-3-羧酸酯类化合物的合成研究备受关注[13-15]。然而，目前国内尚未有大批量规模化生产此类化合物的厂商，导致其价格普遍较高，限制了此类化合物在药物研发方面的需求。因而，开发一种适合 5-取代异噁唑-3-羧酸酯类化合物工业化生产的方法具有重要的现实意义。如下所示，现有文献报道的合成方法[15-18]，多以取代甲基酮（Ⅰ）为起始物，在强碱条件下，例如：正丁基锂（*n*-BuLi）、叔丁醇钾（*t*-BuOK）、氢化钠（NaH）、乙醇钠（EtONa）或甲醇钠（MeONa），与草酸二乙酯生成 *β*-二羰基化合物（Ⅱ），Ⅱ再与盐酸羟胺形成肟（Ⅲ），然后Ⅲ加热成环，得到 5-取代异噁唑-3-羧酸酯（Ⅳ）。这类方法由于原料易得、成本较低而被广泛应用，但其反应步骤长，总收率低而仍有较大的改进空间。



Ⅰ　Ⅱ　Ⅲ　Ⅳ

R=烷基、芳基等取代基

本文拟采用一锅法[16-18]，以烷基或芳基甲基酮类化合物为起始物、甲醇钠为碱催化剂，在单一溶剂甲醇中进行反应，来合成不同取代基的 5-取代异噁唑-3-羧酸甲酯化合物。以期为此类化合物的大规模批量制备提供参考。

1　实验部分

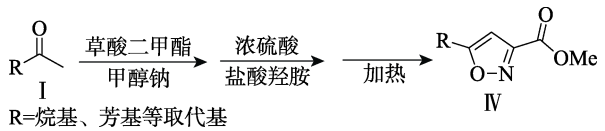
1.1　试剂与仪器

无水甲醇，AR，上海泰坦科技有限公司；浓硫酸（质量分数 98%）、丙酮，AR，河南化之夷科技有限公司；盐酸羟胺、甲醇钠、草酸二甲酯、环丙基甲基酮、频哪酮、苯乙酮、取代苯乙酮、碳酸钾、二碳酸二叔丁酯〔$(Boc)_2O$〕，AR，上海毕得医药科技股份有限公司；三乙胺（TEA）、*t*-BuOK，AR，天津市大茂化学试剂厂；浓盐酸（质量分数 36%），AR，洛阳市化学试剂厂；溴化苄（BnBr）、钯碳（Pd 质量分数 5%），AR，上海麦克林生化科技股份有限公司；硅胶（200~300 目），安徽良臣硅源材料有限公司；石油醚（60~90），AR，济南利扬化工有限公司；乙酸乙酯，AR，上海科醚化学科技有限公司；四氢呋喃，AR，南京一览生物科技有限公司。

Avance 500 MHz 型超导核磁共振波谱仪，德国 Bruker 公司；Finnigan LCQ Advantage MAX 型质谱仪（MS），美国 Thermo Fisher Scientific 公司。

1.2　5-取代异噁唑-3-羧酸甲酯（Ⅳ）的合成

以取代甲基酮为原料，采用一锅法合成 5-取代异噁唑-3-羧酸甲酯（Ⅳ）系列化合物，合成路线如下所示。

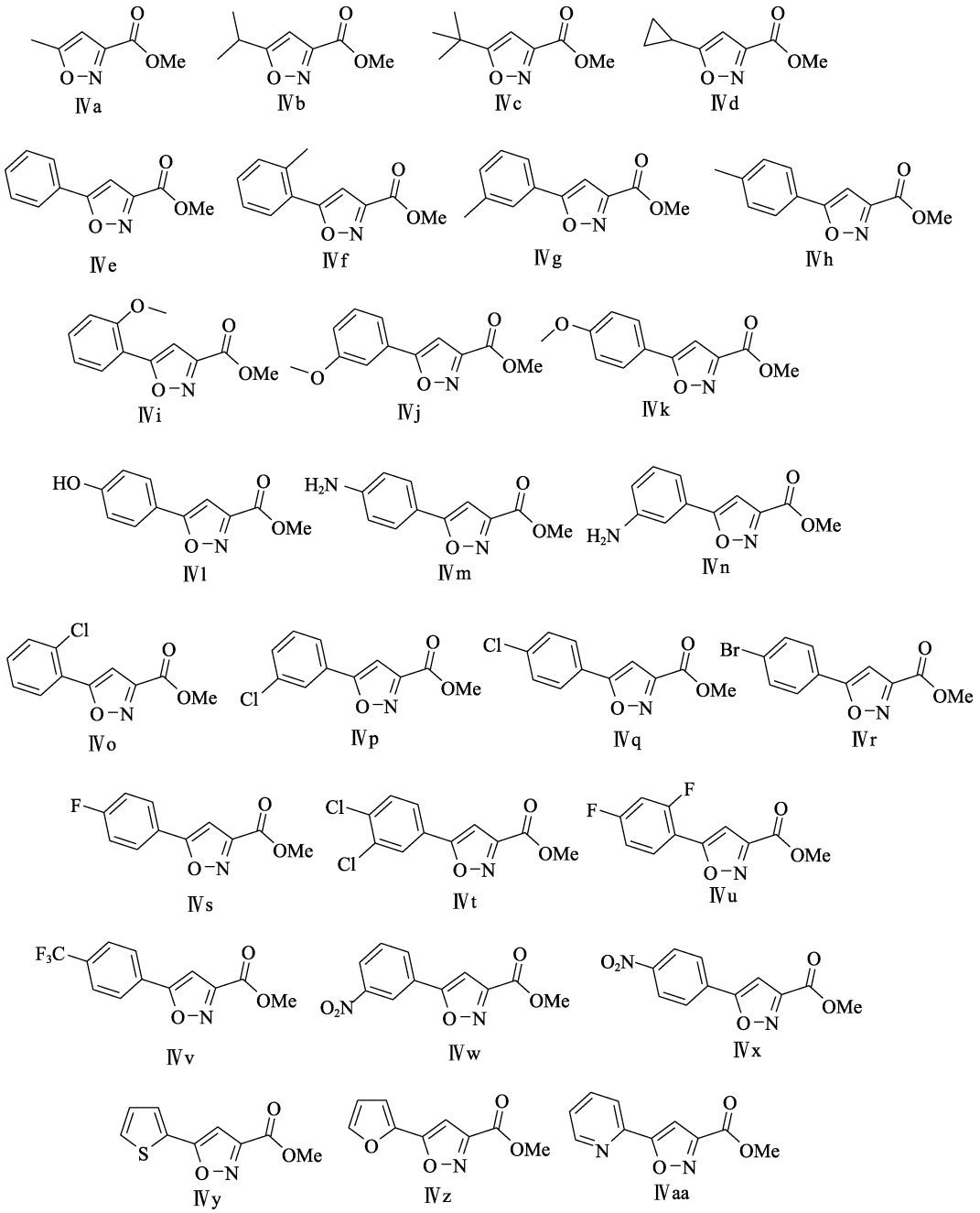


Ⅰ　　Ⅳ

R=烷基、芳基等取代基

向 500 mL 装有机械搅拌、冷凝管、温度计的三口反应瓶中，依次加入甲醇钠 54.0 g（1 mol）、无水甲醇（2 L）。室温搅拌 5 min，加入取代甲基酮（1 mol）和草酸二甲酯 118.0 g（1 mol）的混合溶液，室温搅拌反应 12 h，体系逐渐呈黄色浆状。然后，向反应体系中依次加入浓硫酸 49.0 g（0.5 mol）、盐酸羟胺 69.5 g（1 mol），将反应瓶置于油浴中加热到 80 ℃，搅拌反应 6 h，减压蒸出部分溶剂后冷却，抽滤，滤饼用自来水洗，得 5-取代异噁唑-3-羧酸甲酯类化合物（Ⅳa、Ⅳe~Ⅳaa），Ⅳb~Ⅳd 为液体，需要柱层析纯化，纯化条件为：200~300 目硅胶，洗脱剂为 *V*(石油醚)∶*V*(乙酸乙酯)=3∶1，Ⅳa~Ⅳaa 的分子结构式如下所示。

5-甲基异噁唑-3-羧酸甲酯（Ⅳa）：白色固体，收率为 65%，熔点：98~99 ℃（文献值[19-21]：98~99 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), *δ*: 6.40 (s, 1H), 3.95 (s, 3H), 2.48 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), *δ*: 171.4, 160.5, 156.2, 102.2, 52.7, 12.3。LC 纯度 97% (254 nm)。MS, $C_6H_7NO_3$, *m*/*Z*: $[M+H]^+$理论值 142.12，测试值 142.10；$[M+Na]^+$理论值 164.12，测试值 164.00。



5-异丙基异噁唑-3-羧酸甲酯（Ⅳb）：浅褐色液体[22]，收率为 58%，沸点：160~165 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 6.39 (d, J = 0.6 Hz, 1H), 3.95 (s, 3H), 3.13 (dt, J = 13.9、6.9 Hz, 1H), 1.34 (d, 6H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 168.0, 158.9, 150.0, 100.5, 51.5, 26.0, 23.0。LC 纯度 95% (254 nm)。MS, m/Z: $C_8H_{11}NO_3$[M+H]$^+$ 理论值 170.18，测试值 170.12；[M+Na]$^+$理论值 192.18，测试值 192.01。

5-叔丁基异噁唑-3-羧酸甲酯（Ⅳc）：淡黄色油状液体，收率为 49%，沸点：170~175 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 6.37 (s, 1H), 3.96 (s, 3H), 1.38 (s, 9H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 183.2, 172.6 160.7, 156.1~155.8, 100.3~99.1, 52.6, 28.8~28.2。LC 纯度 95% (254 nm)。MS, $C_9H_{13}NO_3$, m/Z: [M+H]$^+$理论值 184.20,测试值 184.23;[M+Na]$^+$理论值 206.20，测试值 206.14。

5-环丙基异噁唑-3-羧酸甲酯（Ⅳd）：浅褐色液体[23]，收率为 46%，沸点：175~180 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 6.31 (s, 1H), 3.96 (s, 3H), 2.11~2.08 (m, 1H), 1.16~1.08 (m, 2H), 1.03~0.99 (m, 2H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 166.0, 159.0, 152.0, 101.0, 52.0, 9.2, 8.2。LC 纯度 96% (254 nm)。MS, $C_8H_9NO_3$, m/Z: [M+H]$^+$理论值 168.16，测试值 168.13；[M+Na]$^+$理论值 190.16，测试值 190.14。

5-苯基异噁唑-3-羧酸甲酯（Ⅳe）：白色固体，收率为 89%，熔点：81~82 ℃（文献值[24-26]：80~82 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.79~7.77 (m, 2H), 7.48~7.45 (m, 3H), 6.91 (d, 1H), 3.99 (s, 3H);

^{13}CNMR (125 MHz, $CDCl_3$), δ: 171.8, 160.4, 156.6, 130.8, 129.1, 126.5, 125.9, 99.9, 52.9。LC 纯度 98% (254 nm)。MS, $C_{11}H_9NO_3$, *m*/*Z*: $[M+H]^+$ 理论值 204.19，测试值 204.21；$[M+Na]^+$理论值 226.19，测试值 226.21。

5-(2-甲基苯基)异噁唑-3-羧酸甲酯（Ⅳf）：白色固体，收率为 81%，熔点：108~110 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.52~7.51 (m, 2H), 7.25~7.22 (m, 2H), 6.87 (s, 1H), 3.95 (s, 3H), 2.34 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 173.0, 159.4, 156.1, 139.5, 133.7, 127.1, 125.5, 122.1, 98.8, 53.9, 22.4。LC 纯度 97% (254 nm)。MS, $C_{12}H_{11}NO_3$, *m*/*Z*: $[M+H]^+$理论值 218.22，测试值 218.09。

5-(3-甲基苯基)异噁唑-3-羧酸甲酯（Ⅳg）：白色固体，收率为 83%，熔点：118~120 ℃（文献值[27]：118~121 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.54~7.51 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21~7.19 (m, 1H), 6.83 (s, 1H), 3.92 (s, 3H), 2.34 (s, 3H)。^{13}CNMR (125 MHz, $CDCl_3$), δ: 172.0, 160.5, 156.6, 139.0, 131.7, 129.1, 126.5, 123.1, 99.8, 52.9, 21.4。LC 纯度 97% (254 nm)。MS, $C_{12}H_{11}NO_3$, *m*/*Z*: $[M+H]^+$理论值 218.22，测试值 218.04。

5-(4-甲基苯基)异噁唑-3-羧酸甲酯（Ⅳh）：白色固体，收率为 87%，熔点：128~130 ℃（文献值[28] 128~130 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.70 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.85 (s, 1H), 3.98 (s, 3H), 2.38 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 172.1, 160.6, 156.7, 141.4, 129.9, 123.9, 125.9, 99.4, 52.9, 21.6。LC 纯度 97% (254 nm)。MS, $C_{12}H_{11}NO_3$, *m*/*Z*: $[M+H]^+$理论值 218.22，测试值 218.21。

5-(2-甲氧基苯基)异噁唑-3-羧酸甲酯（Ⅳi）：白色固体，收率为 79%，熔点：108~110 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.49~7.39 (m, 3H), 7.10~7.05 (m, 1H), 6.98~6.95 (m, 1H), 4.01 (s, 3H), 3.85 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.7, 169.1, 160.51, 152.5, 142.6, 135.5, 131.9, 118.2, 115.3, 112.0, 56.6, 50.9。LC 纯度 97% (254 nm)。MS, $C_{12}H_{11}NO_4$, *m*/*Z*: $[M+H]^+$理论值 234.22，测试值 234.21。

5-(3-甲氧基苯基)异噁唑-3-羧酸甲酯（Ⅳj）：白色固体，收率为 81%，熔点：111~113 ℃（文献值[29]：112~115 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.43~7.35 (m, 3H), 7.05~7.01 (m, 1H), 6.94~6.91 (m, 1H), 4.02 (s, 3H), 3.89 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.1, 161.6, 150.6, 141.4, 131.3, 130.9, 117.9, 114.9, 111.3, 55.8, 51.5。LC 纯度 97% (254 nm)。MS, $C_{12}H_{11}NO_4$, *m*/*Z*: $[M+H]^+$ 理论值 234.22，测试值 234.21。

5-(4-甲氧基苯基)异噁唑-3-羧酸甲酯（Ⅳk）：白色固体[30]，收率为 85%，熔点：118~120 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.75 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 4.00 (s, 3H), 3.87 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.1, 160.6, 150.6, 130.3, 127.3, 130.9, 118.0, 115.9, 114.3, 58.8, 50.5。LC 纯度 97% (254 nm)。MS, $C_{12}H_{11}NO_4$, *m*/*Z*: $[M+H]^+$理论值 234.22，测试值 234.21。

5-(4-羟基苯基)异噁唑-3-羧酸甲酯（Ⅳl）：白色固体，收率为 45%，熔点：182~184 ℃（文献值[31]：183~186 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 10.17 (s, 1H), 7.78~7.77 (d, 2H), 7.17 (s, 1H), 6.93~6.91 (d, 2H), 3.95 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.7, 168.1, 158.6, 150.3, 129.9, 127.9, 119.9, 116.3, 100.9, 51.5。LC 纯度 96% (254 nm)。MS, $C_{11}H_9NO_4$, *m*/*Z*: $[M+H]^+$理论值 220.19，测试值 220.23。

5-(4-氨基苯基)异噁唑-3-羧酸甲酯（Ⅳm）：黄色固体，收率为 38%，熔点：120~122 ℃（文献值[32] 120~122 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.60 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 7.2 Hz, 2H), 6.72 (s, 1H), 4.05~3.96 (m, 5H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 170.4, 169.8, 152.1, 146.9, 125.4, 118.7, 114.8, 100.4, 51.8。LC 纯度 95% (254 nm)。MS, $C_{11}H_{10}N_2O_2$, *m*/*Z*: $[M+H]^+$理论值 219.21，测试值 219.23。

5-(3-氨基苯基)异噁唑-3-羧酸甲酯（Ⅳn）：黄色固体，收率为 42%，熔点：135~136 ℃（文献值[33]：134~136 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.26 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 1.8 Hz, 1H), 6.87 (s, 1H), 6.78 (dd, *J* = 8.0、1.6 Hz, 1H), 4.07 (s, 3H), 3.85 (bs, 2H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.8, 168.8, 150.5, 149.3, 135.4, 131.7, 118.8, 115.4, 114.8, 99.8, 51.5。LC 纯度 95% (254 nm)。MS, $C_{11}H_{10}N_2O_2$, *m*/*Z*: $[M+H]^+$ 理论值 219.21，测试值 219.21。

5-(2-氯苯基)异噁唑-3-羧酸甲酯（Ⅳo）：白色固体[34]，收率为 82%，熔点：125~128 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 8.01~7.95 (m, 1H), 7.56~7.50 (m, 1H), 7.45~7.38 (m, 2H), 7.36 (d, *J* = 1.3 Hz, 1H), 4.03 (d, *J* = 0.8 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.5, 151.4, 137.3, 132.4, 130.7, 128.5, 127.8, 100.8, 52.0。LC 纯度 98% (254 nm)。MS, $C_{11}H_8ClNO_3$, *m*/*Z*: $[M+H]^+$理论值 238.64，测试值 238.58。

5-(3-氯苯基)异噁唑-3-羧酸甲酯（Ⅳp）：白色固体[35]，收率为 78%，熔点：118~120 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.82 (s, 1H), 7.72 (m, 1H), 7.47 (m, 3H), 4.03 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.2, 168.1, 150.4, 134.8, 131.7, 129.5, 128.8, 127.4, 123.3, 100.5, 51.5。LC 纯度 98% (254 nm)。MS, $C_{11}H_8ClNO_3$, *m*/*Z*: $[M+H]^+$理论值 238.64，测试值 238.58。

5-(4-氯苯基)异噁唑-3-羧酸甲酯（Ⅳq）：白色固体[36]，收率为 83%，熔点：128~130 ℃。^{1}HNMR

(500 MHz, $CDCl_3$), δ: 7.75 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 6.93 (s, 1H), 4.01 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.2, 150.0, 134.3, 129.3, 124.9, 100.5, 51.5。LC 纯度 98% (254 nm)。MS, $C_{11}H_8ClNO_3$, m/Z: $[M+H]^+$理论值 238.64，测试值 238.57。

5-(4-溴苯基)异噁唑-3-羧酸甲酯（Ⅳr）：白色固体，收率为 78%，熔点：138~140 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.67~7.60 (m, 4H), 7.24 (s, 1H), 4.0 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.1, 150.2, 132.3, 127.3, 125.5, 123.1, 100.5, 51.5。LC 纯度 98% (254 nm)。MS, $C_{11}H_8BrNO_3$, m/Z: M+H]$^+$理论值 283.09，测试值 282.94。

5-(4-氟苯基)异噁唑-3-羧酸甲酯（Ⅳs）：白色固体[37]，收率为 75%，熔点：116~118 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 8.04~8.00 (d, 2H), 7.44~7.39 (m, 3H), 3.42 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.2, 168.2, 162.9, 150.1, 127.7, 122.2, 116.1, 100.5, 51.5。LC 纯度 98% (254 nm)。MS, $C_{11}H_8FNO_3$, m/Z: $[M+H]^+$理论值 222.18，测试值 222.21。

5-(3,4-二氯苯基)异噁唑-3-羧酸甲酯（Ⅳt）：白色针状晶体[37]，收率为 78%，熔点：142~145 ℃。^{1}HNMR (500 MHz, DMSO-d_6), δ: 8.30 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 8.5、2.0 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.71 (s, 1H), 3.93 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.5, 160.2, 157.0, 135.3, 133.9, 131.4, 127.8, 126.4, 125.1, 101.0, 53.2。LC 纯度 98% (254 nm)。MS, $C_{11}H_7Cl_2NO_3$, m/Z: $[M+H]^+$理论值 273.08，测试值 272.97。

5-(2,4-二氟苯基)异噁唑-3-羧酸甲酯（Ⅳu）：白色固体[38], 收率为 65%, 熔点: 132~134 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 8.03~7.97 (m, 1H), 7.03~6.96 (m, 3H), 4.02~4.01 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.1, 161.1, 159.9, 150.0, 130.7, 119.1, 111.6, 102.7, 100.5, 52.0。LC 纯度 98% (254 nm)。MS, $C_{11}H_7F_2NO_3$, m/Z: $[M+H]^+$理论值 240.18，测试值 240.21。

5-(4-三氟甲基苯基)异噁唑-3-羧酸甲酯（Ⅳv）：类白色固体[39]，收率为 62%，熔点：135~137 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 8.19~8.17 (d, 2H), 7.92 (d, 2H), 7.62 (s, 1H), 3.37 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.1, 150.0, 124.3, 129.9, 125.6, 125.3, 100.5, 51.5。LC 纯度 98% (254 nm)。MS, $C_{12}H_8F_3NO_3$, m/Z: $[M+H]^+$理论值 272.19，测试值 272.21。

5-(3-硝基苯基)异噁唑-3-羧酸甲酯（Ⅳw）：淡黄色固体, 收率为 38%, 熔点: 158~160 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 8.65 (s, 1H), 8.33 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.73~7.70 (m, 1H), 7.09 (s, 1H), 4.02 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.2, 160.0, 157.1, 148.8, 131.5, 130.6, 128.1, 125.3, 121.0, 101.8, 53.2。LC 纯度 97% (254 nm)。MS, $C_{11}H_8N_2O_5$, m/Z: $[M+H]^+$理论值 249.19，测试值 249.21。

5-(4-硝基苯基)异噁唑-3-羧酸甲酯（Ⅳx）：淡黄色固体[40]，收率为 40%，熔点：178~180 ℃。^{1}HNMR (500 MHz, $CDCl_3$), δ: 8.39 (d, 2H), 8.25 (d, 2H), 7.81 (s, 1H), 3.32 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 169.3, 168.1, 150.1, 147.8, 132.7, 124.5, 100.1, 51.2。LC 纯度 97% (254 nm)。MS, $C_{11}H_8N_2O_5$, m/Z: $[M+H]^+$理论值 249.19，测试值 249.22。

5-(2-噻吩基)异噁唑-3-羧酸甲酯（Ⅳy）：类白色固体，收率为 82%，熔点：86~88 ℃（文献值[41]：86~88 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.57 (dd, J = 3.7、1.2 Hz, 1H), 7.51 (dd, J = 5.0、1.1 Hz, 1H), 7.16 (dd, J = 5.1、3.7 Hz, 1H), 6.79 (s, 1H), 4.00 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 168.1, 158.9, 150.0, 133.7, 128.0, 124.0, 122.5, 98.5, 50.0。LC 纯度 99% (254 nm)。MS, $C_9H_7NO_3S$, m/Z: $[M+H]^+$理论值 210.22，测试值 210.22。

5-(2-呋喃基)异噁唑-3-羧酸甲酯（Ⅳz）：棕色固体，收率为 92%，熔点：68~70 ℃（文献值[42]：69~70 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 7.96~7.95 (d, 1H), 7.56 (d, 1H), 7.25 (s, 1H), 6.63~6.54 (m, 1H), 3.97 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 163.2, 160.1, 156.3, 144.7, 142.2, 112.0, 111.4, 99.3, 52.9。LC 纯度 98% (254 nm)。MS, $C_9H_7NO_4$, m/Z: $[M+H]^+$理论值 194.16，测试值 194.14；$[M+Na]^+$理论值 216.16，测试值 216.06。

5-(2-吡啶基)异噁唑-3-羧酸甲酯（Ⅳaa）：黄色固体，收率为 48%，熔点：70~72 ℃（文献值[43]：72~74 ℃）。^{1}HNMR (500 MHz, $CDCl_3$), δ: 8.72 (d, J = 4.5 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.86 (dt, J = 8.0、1.5 Hz, 1H), 7.40~7.37 (m, 1H), 7.31 (s, 1H), 4.02 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$), δ: 171.1, 160.2, 156.9, 150.3, 145.8, 137.2, 124.9, 121.1, 102.7, 52.9。LC 纯度 95% (254 nm)。MS, $C_{10}H_8N_2O_3$, m/Z: $[M+H]^+$理论值 205.18，测试值 205.21。

2　结果与讨论

2.1　工艺条件的优化

2.1.1　碱和溶剂的选择

按照 1.2 节实验方法，第一步酮类和草酸二甲酯的 Claisen 缩合反应在无水甲醇中进行，需要强碱催化。经过大量实验发现，甲醇钠可以满足反应的要求。虽然其他碱（如 n-BuLi、t-BuOK、NaH 等）的碱性比甲醇钠更强，但是需要四氢呋喃作溶剂，而四氢呋喃的价格大约是无水甲醇的 4~5 倍。所以，从产物总收率、反应安全性和合成成本综合考虑，

甲醇钠的实用性、性价比更高。另外，后续的成肟、脱水成环反应，甲醇也都适合作反应溶剂。因此，选择甲醇钠作碱，可以统一整个反应过程的溶剂，使整个合成过程在同一种溶剂中进行，节约成本，便于回收溶剂。

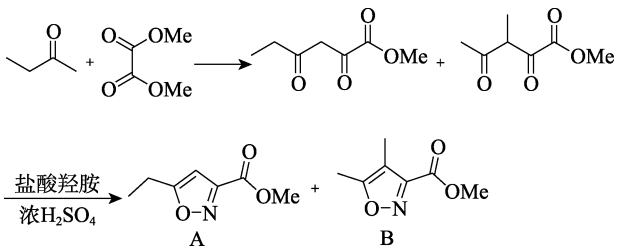
2.1.2　酸的选择

酮和草酸酯缩合反应后，得到 *β*-二羰基化合物的钠盐形式，此步需要用酸中和后才能进行下一步成肟、成环反应。经考察盐酸、醋酸、硫酸等，发现盐酸含水量大，会发生产物甲酯水解的副反应；醋酸因为酸性较弱，导致成环时间延长，且成环收率较低；浓硫酸的效果最好，浓硫酸仅含的质量分数 2%水分对该反应几乎无影响，且硫酸钠副产物伴随产物一起析出后，用少量水洗涤即可除去，虽有少量废水，但废水成分单一，易于处理。

2.2　不同取代基的影响

在不同 5-取代异噁唑-3-羧酸甲酯的合成过程中，脂肪类取代基和芳香类取代基有明显的区别。这是因为，脂肪类甲基酮因脂肪取代基的供电子性，钝化了自身羰基，芳香酮因为芳香环的吸电性效应活化了自身羰基，因此芳香酮的反应活性高于脂肪酮，所以芳香取代基类的异噁唑收率较高。

在制备某些脂肪类取代的异噁唑-3-羧酸甲酯类化合物时，如 5-乙基异噁唑-3-羧酸甲酯和 5-异丙基异噁唑-3-羧酸甲酯，都发现了异构化现象。这是由于该类酮为不对称烷酮，羰基的两侧均可发生 Claisen 缩合。如下所示，以 5-乙基异噁唑-3-羧酸甲酯为例，以丁酮为起始原料，最后得到的是质量比为 1∶1 的 5-乙基异噁唑-3-羧酸甲酯（A）和 4,5-二甲基异噁唑-3-羧酸甲酯（B）混合物，且易于分离；制备 5-异丙基异噁唑-3-羧酸甲酯时，虽然也有少量的异构化，但异构体质量所占比例相对不多，大约 10%。



呋喃、噻吩等五元杂环酮反应活性也较高，缺电子的吡啶酮类反应活性稍弱一些。

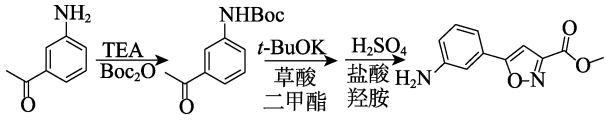
2.3　5-取代异噁唑-3-羧酸甲酯的合成

2.3.1　5-叔丁基异噁唑-3-羧酸甲酯（Ⅳc）

在合成 5-叔丁基异噁唑-3-羧酸甲酯（Ⅳc）时，因为频哪酮中叔丁基位阻的影响，其反应活性偏低，需要使用碱性更强的 *t*-BuOK 代替甲醇钠作催化剂，反应在四氢呋喃中进行，得到液体 5-叔丁基异噁唑-3-羧酸甲酯（Ⅳc），最终产物需要柱层析纯化。

2.3.2　5-(3-氨基苯基)异噁唑-3-羧酸甲酯（Ⅳn）

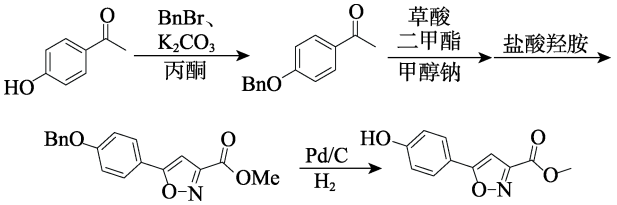
合成 5-(3-氨基苯基)异噁唑-3-羧酸甲酯（Ⅳn）时，氨基需要叔丁氧羰基（Boc）保护。与草酸二甲酯的酯缩合反应也需碱性较强的 *t*-BuOK，反应在四氢呋喃中进行。因成环过程为酸性环境，Boc 保护基会在成环时离去，合成路线如下所示。



5-(4-氨基苯基)异噁唑-3-羧酸甲酯（Ⅳm）与其合成方法相同。

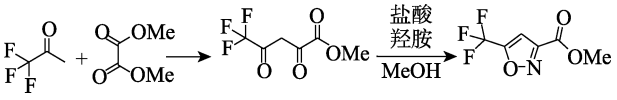
2.3.3　5-(4-羟基苯基)异噁唑-3-羧酸甲酯（Ⅳl）

合成 5-(4-羟基苯基)异噁唑-3-羧酸甲酯（Ⅳl），需要对酚羟基进行苄醚化保护，成环后钯碳氢化脱除苄基。合成路线如下所示。

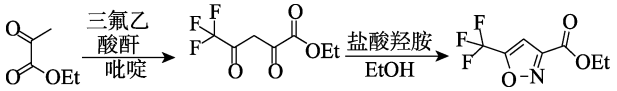


2.3.4　5-三氟甲基异噁唑-3-羧酸甲酯（Ⅳv）

5-三氟甲基异噁唑-3-羧酸甲酯（Ⅳv）的合成，采用如下所示的合成路线，未获成功；分别采用不同的碱（甲醇钠、*t*-BuOK、NaH），但均未成功。



此外，也采取了以三氟乙酸酐和丙酮酸乙酯为原料，对合成路线进行修正，如下所示，分别采用不同的碱（吡啶、甲醇钠、*t*-BuOK、NaH）也均未获成功，最后仅仅得到的是丙酮酸乙酯和盐酸羟胺形成的肟。



3　结论

通过一锅法合成了 26 种 5-取代异噁唑-3-羧酸酯类化合物，结论如下：

（1）完成了大部分 5-取代异噁唑-3-羧酸酯类化

合物的合成，减少了中间体的处理过程，节约了物料成本，方法简捷高效；同时，大多数化合物的反应过程只使用无水甲醇作溶剂，易于回收；避免使用碱性更强的碱，更加安全、易于操作。

（2）制备 5-取代异噁唑-3-羧酸酯类化合物的方法具有普适性，最终产物易于纯化，大部分 5-取代异噁唑-3-羧酸甲酯为固体（仅有 3 个为液体产物），在反应结束后，产物多以晶体形式析出，无需进一步纯化即可达到 95%以上的纯度，简化了提纯流程，总体收率较高，具有一定的工业化前景。

（3）有个别烷烃取代的 5-取代异噁唑-3-羧酸酯化合物存在异构现象，需要优化完善；5-三氟甲基异噁唑-3-羧酸酯尚未成功制备，需要设计新的合成方法和条件。

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