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Solvent-free one-pot synthesis of 2-pyridone derivatives

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Abstract

An efficient synthesis of methyl 4-hydroxy-6-oxo-1,6-dihydro-2-pyridine carboxylates is described. This involves three component reactions between primary alkyl amines, malonyl dichloride and methyl propiolates.

Keywords: One-pot reactions; Multicomponent reactions; Methyl propiolate; Green chemistry

The methods of green chemistry continue to grow in importance. Alternative processes help to conserve resources and can even reduce costs. The replacement of convention solvents with water or solvent-free conditions, which is harmless to health and is available in large quantities, is one of the most interesting basic approaches along these lines. The 2-pyridone core structure is an important heterocyclic framework that can be found in numerous biologically active compounds. It is also a versatile synthon that can be further transformed to pyridine, piperidine, quinolizidine, and indolizidine alkaloids [1]. *N*-Alkylated 2-pyridones are important intermediates in the synthesis of polycyclic compounds of biological significance [2]. The broad range of applications of the 2-pyridone structural motif has resulted in several synthetic methods [3]. The most versatile and useful strategy to produce pyridine derivatives is condensation between 1,3-dicarbonyl compounds and 3-aminoenones,3-aminoacrylates, or cyanoacetamides [4,5]. Recently, multicomponent condensation reactions have become a powerful method for the synthesis of small-molecule libraries, due to the fact that products are formed in a single step by simultaneous reactions of several reagents and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component [6–8]. Herein, we describe an efficient synthesis of functionalized 2-pyridones *via* the reaction of alkyl amines **1** with methyl propiolate **2** in the presence of malonyl dichloride **3** under solvent-free conditions at 50°C (Scheme 1).

The structures of compounds **4a–g** were apparent from the ^{1}H NMR, ^{13}C NMR and IR spectra which are in agreement with the proposed structures [9]. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed five singlets for methoxy (δ 3.75), methylene (δ 5.20), methine (δ 6.12 and 6.27), and OH (δ 10.75) protons, along with characteristic multiplets for the aromatic protons. The ^{13}C NMR spectrum of **4a** exhibited 12 signals in agreement with the proposed structure.

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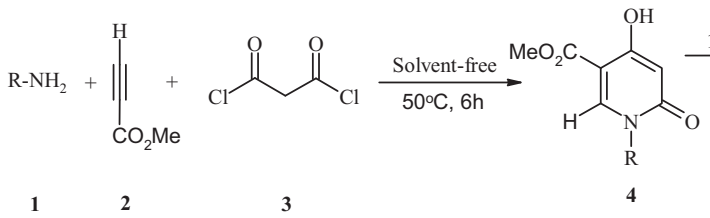
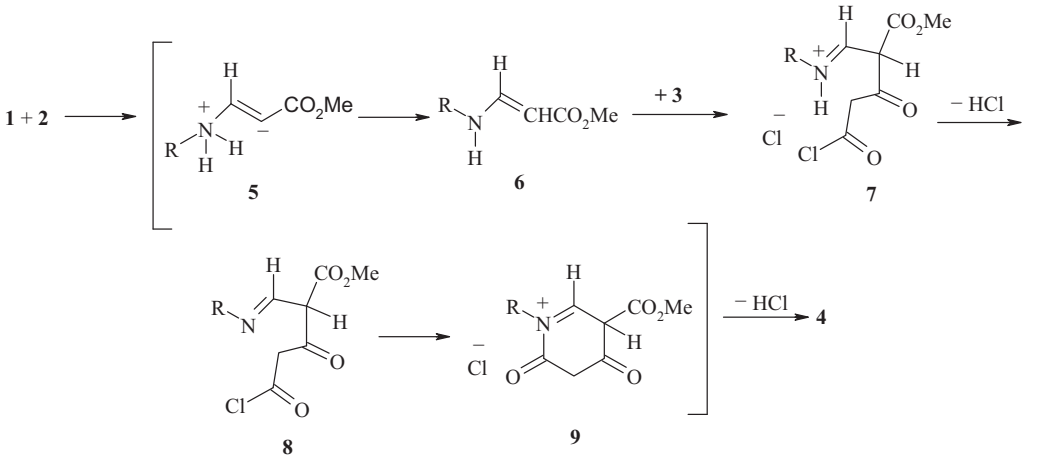


1, 2, 4	R	Yield (%) of 4
a	Bn	92
b	4-Me-C_6H_4-CH_2	90
c	4-MeO-C_6H_4-CH_2	87
d	4-Cl-C_6H_4-CH_2	89
e	2-Me-C_6H_4-CH_2	92
f	1-naphthylmethyl	90
g	*n*-Butyl	90

Scheme 1. Three component reaction of alkyl amines with methyl propiolate in the presence of malonyl dichloride.



Scheme 2. Proposed mechanism for the one-pot synthesis of 2-pyridones.

The ^{1}H NMR and ^{13}C NMR spectra of **4b–g** were similar to those of **4a** which showed characteristic resonances in appropriate regions of the spectrum. A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of enaminone **6** from the amine and propiolate [10,11] which is subsequently attacked by malonyl dichloride to produce **7**. Intermediate **7** undergoes cyclization reaction, HCl elimination and keto-enol tautomerism to generate **4**.

In conclusion, we have described a convenient route to functionalized 2-pyridones, from malonyl dichloride and methyl propiolate in the presence of primary amines. The advantage of the present procedure is that the reaction is performed under solvent-free conditions by simple mixing of the starting materials. The procedure described here provides an acceptable one-pot method for the preparation of functionalized 2-pyridones.

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References

[1] (a) J. Lazaar, C. Hoarau, F. Mongin, et al. Tetrahedron Lett. 46 (2005) 3811;
(b) N. Pemberton, L. Jakobsson, F. Almqvist, Org. Lett. 8 (2006) 936;
(c) D.L. Comins, J.M. Nolan, Org. Lett. 3 (2001) 4255;
(d) H. Josein, S.B. Ko, D. Bom, et al. Chem. Eur. J. 4 (1998) 67;
(e) D.L. Comins, J.K. Saha, J. Org. Chem. 61 (1996) 9623;
(f) D. Villemin, L. Liao, Tetrahedron Lett. 37 (1996) 8733.

[2] (a) N.S. Cutshall, K.A. Kucera, R. Ursion, et al. Bioorg. Med. Chem. Lett. 12 (2002) 1517;
(b) D. Gaskell, Chem. Ber. 34 (1998) 27.
[3] (a) G.D. Henry, Tetrahedron 60 (2004) 6043;
(b) D. Bevk, R. Jakše, L. Golobič, et al. Heterocycles 63 (2004) 609;
(c) B. Stanovnik, J. Svete, Chem. Rev. 104 (2004) 2433;
(d) D.S. Coffey, S.P. Kolis, S.A. May, Prog. Heterocycl. Chem. 15 (2003) 284.
[4] (a) A. Arcadi, M. Chiarani, S. Di Giuseppe, F. Marinelli, Synlett (2003) 203;
(b) S.A. Petrich, F.A. Hicks, D.R. Wilkinson, et al. Tetrahedron 51 (1995) 1575.
[5] J.A. Varela, C. Saá, Chem. Rev. 103 (2003) 3787.
[6] (a) A. Dömling, I. Ugi, Angew. Chem. Int. Ed. 39 (2000) 3168;
(b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, Chem. Eur. J. 6 (2000) 3321;
(c) D. Lee, J.K. Sello, S.L. Schreiber, Org. Lett. 2 (2000) 709;
(d) A. Domling, Chem. Rev. 106 (2006) 17;
(e) I. Ugi, J. Prakt. Chem. 339 (1997) 499;
(f) R.W. Armstrong, A.P. Combs, P.A. Tempest, et al. Acc. Chem. Res. 29 (1996) 123.
[7] F. Rostami, Z. Hossaini, B. Mohtat, et al. Chin. Chem. Lett. 22 (2011) 1143.
[8] M.A. Khalilzadeh, A. Hasannia, M.M. Baradarani, et al. Chin. Chem. Lett. 22 (2011) 49.
[9] *General procedure for preparation of compounds* **4a–g.** To a mixture of alkyl propiolate (2.5 mmol) and primary amine (2.5 mmol) malonyl dichloride (0.19 mL, 2 mmol) was added slowly at 50 °C. The reaction mixture was then stirred for 6 h. The reaction mixture was purified by flash column chromatography on silica gel (Merck 230–400 mesh) using n-hexane–EtOAc as eluent to afforded pure compounds. *Methyl 1-benzyl-4-hydroxy-6-oxo-1,6-dihydro-2-pyridinedicarboxylate* (**4a**). White powder; mp 114–116 °C; yield: 0.48 g (92%). IR (KBr): 3442 (OH), 1730, 1627, 1542, 1385 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 3 H, MeO), 5.20 (s, 2 H, CH_2), 6.12 (s, 1 H, CH), 6.27 (s, 1 H, CH), 7.14 (d, 2 H, ^3J = 7.0 Hz, 2 CH), 7.24–7.30 (m, 3 H, 3 CH), 10.75 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.8 (NCH_2), 52.8 (MeO), 97.8 (CH), 100.2 (CH), 102.6 (C), 127.4 (2 CH), 128.0 (CH), 128.6 (2 CH), 135.5 (C), 162.5 (C), 165.3 (C=O), 167.1 (C=O). MS: *m/z* (%) = 259 (15) [M^+], 228 (64), 168 (15), 91 (100), 77 (20), 31 (28). Anal. Calcd for $C_{14}H_{13}NO_4$ (259.26): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.12; N, 5.45. *Methyl 1-(4-methylbenzyl)-4-hydroxy-6-oxo-1,6-dihydro-2-pyridine dicarboxylate* (**4b**). White powder; mp 119–121 °C; yield: 0.49 g (90%). IR (KBr): 3445 (OH), 1734, 1635, 1584, 1373 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.45 (s, 3H, Me), 3.82 (s, 3 H, MeO), 5.24 (s, 2 H, CH_2), 6.15 (s, 1 H, CH), 6.34 (s, 1 H, CH), 7.15 (d, 2 H, ^3J = 7.3 Hz, 2 CH), 7.30 (d, 2 H, ^3J = 7.3 Hz, 2 CH), 10.68 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5 (CH_3), 48.2 (NCH_2), 53.0 (MeO), 98.2 (CH), 100.4 (CH), 105.7 (C), 127.5 (2 CH), 128.4 (2 CH), 130.7 (C), 135.4 (C), 160.7 (C), 165.5 (C=O), 167.6 (C=O). *Methyl 1-(4-methoxylbenzyl)-4-hydroxy-6-oxo-1,6-dihydro-2-pyridine dicarboxylate* (**4c**). White powder; mp 128–130 °C; yield: 0.50 g (87%). IR (KBr): 3440 (OH), 1737, 1636, 1580, 1287 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 3H, MeO), 3.89 (s, 3 H, MeO), 5.25 (s, 2 H, CH_2), 6.08 (s, 1 H, CH), 6.23 (s, 1 H, CH), 7.08 (d, 2 H, ^3J = 7.5 Hz, 2 CH), 7.45 (d, 2 H, ^3J = 7.6 Hz, 2 CH), 10.75 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 48.5 (NCH_2), 52.8 (CH_3O), 53.3 (OMe), 98.5 (CH), 99.7 (CH), 104.8 (C), 117.4 (2 CH), 131.7 (2 CH), 135.4 (C), 154.4 (C), 158.7 (C), 164.6 (C=O), 168.2 (C=O). *Methyl 1-(4-chlorobenzyl)-4-hydroxy-6-oxo-1,6-dihydro-2-pyridine dicarboxylate* (**4d**). White powder; mp 138–140 °C; yield: 0.52 g (89%). IR (KBr): 3452 (OH), 1733, 1645, 1557, 1235 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 3H, MeO), 5.14 (s, 2 H, CH_2), 6.12 (s, 1 H, CH), 6.27 (s, 1 H, CH), 7.16 (d, 2 H, ^3J = 7.8 Hz, 2 CH), 7.32 (d, 2 H, ^3J = 7.8 Hz, CH), 10.82 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.2 (NCH_2), 53.3 (OMe), 97.4 (CH), 99.5 (CH), 106.7 (C), 125.4 (2 CH), 131.5 (2 CH), 137.4 (C), 140.4 (C), 159.4 (C), 165.0 (C=O), 168.5 (C=O). *Methyl 1-(2-methylbenzyl)-4-hydroxy-6-oxo-1,6-dihydro-2-pyridine dicarboxylate* (**4e**). White powder; mp 125–127 °C; yield: 0.50 g (92%). IR (KBr): 3450 (OH), 1738, 1647, 1489, 1325 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.52 (s, 3H, Me), 3.85 (s, 3 H, MeO), 5.27 (s, 2 H, CH_2), 6.18 (s, 1 H, CH), 6.35 (s, 1 H, CH), 6.78 (d, 1 H, ^3J = 7.4 Hz, CH), 7.05 (d, 1 H, ^3J = 7.3 Hz, CH), 7.34 (t, 2 H, ^3J = 7.5 Hz, 2 CH), 10.79 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.4 (CH_3), 48.7 (NCH_2), 53.2 (OMe), 100.2 (CH), 100.5 (CH), 110.4 (C), 125.4 (CH), 128.2 (CH), 128.9 (CH), 130.4 (CH), 131.4 (C), 139.4 (C), 156.7 (C), 163.8 (C=O), 167.5 (C=O). *Methyl 1-(1-naphthylmethyl)-4-hydroxy-6-oxo-1,6-dihydro-2-pyridine dicarboxylate* (**4f**). Pale yellow powder; mp 137–139 °C; yield: 0.56 g (90%). IR (KBr): 3452 (OH), 1742, 1598, 1365, 1287 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 3 H, MeO), 5.24 (s, 2 H, CH_2), 6.23 (s, 1 H, CH), 6.45 (s, 1 H, CH), 7.27 (d, 1 H, ^3J = 7.3 Hz, CH), 7.32 (t, 1 H, ^3J = 7.3 Hz, CH), 7.34 (t, 1 H, ^3J = 7.5 Hz, CH), 7.74 (t, 1 H, ^3J = 7.5 Hz, CH), 7.85 (d, 1 H, ^3J = 7.4 Hz, CH), 8.02 (t, 1 H, ^3J = 7.5 Hz, CH), 8.67 (t, 1 H, ^3J = 7.5 Hz, CH), 11.29 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.5 (NCH_2), 52.7 (OMe), 105.2 (CH), 111.4 (CH), 124.5 (CH), 125.3 (C), 126.7 (CH), 127.2 (3 CH), 128.7 (CH), 130.2 (CH), 131.7 (C), 135.4 (C), 140.7 (C), 160.7 (C), 164.5 (C=O), 168.3 (C=O). *Methyl 1-butyl-4-hydroxy-6-oxo-1,6-dihydro-2-pyridinedicarboxylate* (**4g**). Yellow powder; mp 107–109 °C; yield: 0.56 g (90%). IR (KBr): 3435 (OH), 1737, 1625, 1478, 1325 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.02 (t, 3 H, ^3J = 7.3 Hz, Me), 1.34 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 3.25 (t, 3 H, ^3J = 7.4 Hz, NCH_2), 3.86 (s, 3 H, MeO), 5.96 (s, 1 H, CH), 6.24 (s, 1 H, CH), 10.85 (s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2 (CH_3), 21.2 (CH_2), 32.0 (CH_2), 48.3 (NCH_2), 52.8 (OMe), 106.7 (CH), 110.5 (CH), 135.4 (C), 158.7 (C), 165.3 (C=O), 167.6 (C=O).
[10] (a) R. Huisgen, K. Herbig, A. Siege1, H. Huber, Chem. Ber. 99 (1966) 2526;
(b) K. Herbig, R. Huisgen, H. Huber, Chem. Ber. 99 (1966) 2540.
[11] (a) I. Yavari, A. Hossein-Nia, Magn. Reson. Chem. 30 (1992) 413;
(b) I. Yavari, A. Shaabani, H. Soliemani, et al. Magn. Reson. Chem. 34 (1996) 1003.