Simple and Efficient Access to 3-Ethoxycarbonylpyrroles, Benzofurans, and Naphthofurans

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Received 29 April 2009; revised 11 August 2009

Abstract: An efficient method was developed for the synthesis of pyrrole and furan derivatives from enamines, phenols, and naphthols. The key steps involve iodocyclization and alumina-induced dehydroiodination reactions.

Key words: alumina, dehydroiodination, heterocycles, iodocyclization, ultrasound

Pyrrole and furan derivatives are important classes of five-membered heterocycles found in many natural products.1,2 They have attracted much attention because of their broad spectrum of pharmacological activities, including antineoplastic,3 antipsychotic,4 antimicrobial, antioxidant, and anti-retroviral activities.5 These compounds can be readily prepared by iodine-promoted cyclization of functionally substituted alkenes.6,7 For example, we have previously reported a synthesis of pyrroles by iodocyclization of allyl bromide (Scheme 2) and a reactant because it can be easily removed by filtration at the end of the preparation and recycled.

The method was also used for the synthesis of benzo- furans and naphthofuran derivatives. Thus, reaction of phenols 6,10 and 911 and naphthols 1212 and 1510 with iodine, followed by treatment with alumina with heating gave the corresponding products 8,13 11,14 14,13 and 17,7 respectively (Scheme 2 and Scheme 3).

Finally, this method was extended to the synthesis of 2,4-dimethylfuro[3,2-c]quinoline (20),16 3-Allyl-2-methylquinolin-4-ol (18), which we recently prepared,17 underwent iodocyclization to give dihydrofuran derivative 1911 in excellent yield. Dehydroiodination of 19, as described above, gave the desired product, as shown in Scheme 4.

As shown in Scheme 5, we propose that an intermediate A may be involved in the reaction; because of its basic character, alumina may abstract a proton to give an exometh-
ylene intermediate B, which aromatizes to give the product C.

The simplicity of the whole process, the ready availability of starting materials, and the high overall yield make this strategy very attractive for the synthesis of this very important group of heterocyclic compounds, which can serve key intermediates for the synthesis of several biologically active products.

1H NMR and 13C NMR spectra were recorded with a Bruker DPX300 spectrometer operating at 300 MHz and 75 MHz, respectively, in CDCl3 as a solvent with TMS as an internal standard. Chemical shifts are reported in ppm (δ units). Coupling constants are reported in units of hertz (Hz), if applicable. IR spectra were recorded with a Bomem MB100-FTIR spectrometer, measured in percentage of transmittance (% T) on samples prepared as films or KBr pellets. All GC/MS studies were performed on a Shimadzu 14B/QP5050A with a DB1 column (30 m). For liquid chromatography, 70–230 mesh silica gel (Merck) was used as the stationary phase.

**Ethyl-2-acetylpent-4enoate (2)**
A mixture of ethyl acetoacetate (I: 10.5 mmol), LiOH (10.5 mmol), H2O (2 mL), and allyl bromide (10.0 mmol) was placed in an ultrasound bath (USC 700, 40 KHz) for 15 min. The mixture was then extracted with EtOAc (20 mL), dried (anhyd Na2SO4), and concentrated under reduced pressure.

**Ethyl 5-(iodomethyl)-2-methyl-1-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate (4a)**
Yield: 75%.

**Iodocyclization; General Procedure**
A soln of the substituted alkene derivative (5 mmol) in CH2Cl2 (25 mL) was treated with NaHCO3 (5.5 mmol) and I2 (5.5 mmol). The mixture was stirred at r.t. for 24 h then extracted with EtOAc. The combined organic layers were washed sequentially with aq Na2S2O3 mixture was stirred at r.t. for 24 h then extracted with EtOAc. The combined organic layers were washed sequentially with aq Na2S2O3 and sat. aq NaCl, dried (MgSO4), and concentrated under reduced pressure.

**Ethyl 5-(iodomethyl)-2-methyl-1-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate (4b)**
Yield: 85%.

1H NMR (300 MHz, CDCl3): δ = 1.27 (t, J = 7.1 Hz, 3 H), 2.29 (s, 3 H), 2.53 (dd, J = 7.2, 15.1 Hz, 1 H), 3.04 (dd, J = 11.2, 15.1 Hz, 1 H), 3.10–3.20 (m, 2 H), 3.54–3.67 (m, 1 H), 4.25 (d, J = 16.8 Hz, 1 H), 4.52 (d, J = 16.8 Hz, 1 H), 7.14–7.35 (m, 5 H).

13C NMR (75 MHz, CDCl3): δ = 10.9, 12.3, 14.6, 35.2, 47.9, 58.6, 60.7, 95.7, 126.7, 127.5, 128.8, 137.1, 159.6, 166.7.

**Ethyl 1-Benzyl-5-(iodomethyl)-2-methyl-4,5-dihydro-1H-pyrrole-3-carboxylate (4c)**
Yield: 80%.

IR (film): 1687, 1585, 1081 cm–1.

1H NMR (300 MHz, CDCl3): δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.25–1.38 (m, 6 H), 1.50–1.60 (m, 2 H), 2.05 (s, 3 H), 2.50 (dd, J = 7.5, 15.0 Hz, 1 H), 3.00 (dd, J = 11.0, 15.0 Hz, 1 H), 3.08–3.17 (m, 2 H), 3.20 (t, J = 7.0 Hz, 2 H), 4.00–4.13 (m, 1 H), 4.15 (q, J = 7.1 Hz, 2 H).

13C NMR (75 MHz, CDCl3): δ = 10.9, 12.3, 14.6, 35.2, 47.9, 58.6, 60.7, 95.7, 126.7, 127.5, 128.8, 137.1, 159.6, 166.9.

**Ethyl 1-Hexyl-5-(iodomethyl)-2-methyl-4,5-dihydro-1H-pyrrole-3-carboxylate (4d)**
Yield: 80%.

IR (film): 1687, 1585, 1081 cm–1.
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1H NMR (75 MHz, CDCl3): δ = 11.3, 12.3, 13.8, 14.1, 22.4, 26.5, 27.4, 31.0, 35.9, 43.6, 59.2, 61.4, 110.1, 157.9, 166.9.

Anal. Calcd for C14H14NO2: C, 71.67; H, 10.03; N, 5.57. Found: C, 73.42; H, 8.59; N, 5.44.

1V C NMR (75 MHz, CDCl3): δ = 8.2 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.93 (d, J = 8.9 Hz, 1 H).

2-(Iodomethyl)-5-methoxy-2,3-dihydro-1-benzofuran (7)

Yield: 80%.

IR (KBr): 1644, 1592, 1550, 1505, 1331, 1158 cm–1.

Yield: 85%.

2-(Iodomethyl)-2,3-dihydro-1-benzofuran (13)

Yield: 80%.

IR (KBr): 1701, 1692, 1606, 1581 cm–1.

Yield: 80%.

2-(Iodomethyl)-1,2-dihydronaphtho[1,2-b]furan (16)

Yield: 80%.

IR (KBr): 1701, 1692, 1606, 1581 cm–1.

Yield: 85%.

Ethyl 1-Benzyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (5a)

Yield: 80%.

IR (KBr): 1697, 1580, 1230, 1085 cm–1.

Yield: 80%.

1V C NMR (75 MHz, CDCl3): δ = 12.1, 12.6, 14.3, 58.9, 107.5, 111.5, 128.0, 128.4, 129.7, 136.0, 137.7, 165.6.


Dehydroiodination; General Procedure

Neutral activated Al2O3 (Merk 70–230 mesh; 30 g) was added to a stirred solution of the cyclic iodine derivative (1 mmol) in CH2Cl2 (20 mL). The solvent was removed under vacuum, and the mixture was heated at 160 °C for 15 min then cooled to r.t. CH2Cl2 (10 mL) was added, the Al2O3 was removed by Büchner filtration, and the organic phase was evaporated under vacuum.

Ethyl 2,5-Dimethyl-1-phenyl-1H-pyrrole-3-carboxylate (5b)

Yield: 85%.

IR (KBr): 1697, 1580, 1230, 1085 cm–1.

Yield: 80%.

5-Methoxy-2-methyl-1-benzofuran (8)

IR (KBr): 1701, 1692, 1606, 1581 cm–1.

Ethyl 1-Hexyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (5c)

Yield: 80%.

IR (KBr): 1697, 1580, 1230, 1085 cm–1.

5-Methoxy-2-methyl-1-phenol (8a)

Yield: 82%.

IR (KBr): 2715, 1705, 1655, 1580, 1105 cm–1.

Yield: 80%.

IR (KBr): 2715, 1715, 1660, 1573, 1110 cm–1.

Yield: 80%.

7-Methoxy-2-methyl-1-benzofuran-5-carboxaldehyde (11)


Synthesis 2009, No. 23, 3963–3966 © Thieme Stuttgart · New York
2-Methylnaptho[1,2-b]furan (14)

Yield: 81%.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.52$ (d, $J = 1.0$ Hz, 3 H), 6.45 (q, $J = 1.1$ Hz, 3 H), 7.43 (t, $J = 8.2$ Hz, 1 H), 7.53 (d, $J = 8.2$ Hz, 1 H), 7.60 (d, $J = 8.0$ Hz, 1 H), 7.80 (d, $J = 8.0$ Hz, 1 H), 8.09 (d, $J = 8.2$ Hz, 1 H), 8.20 (s, 1 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): 122.5, 126.9, 128.4, 129.4, 130.1, 150.0, 154.4.

2-Methylfuran (17)

Yield: 85%.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 2.52$ (d, $J = 1.1$ Hz, 3 H), 6.45 (q, $J = 1.1$ Hz, 1 H), 7.41 (t, $J = 8.2$ Hz, 1 H), 7.53 (t, $J = 8.2$ Hz, 1 H), 7.58 (d, $J = 8.5$ Hz, 1 H), 7.80 (d, $J = 8.0$ Hz, 1 H), 8.09 (d, $J = 8.2$ Hz, 1 H), 8.20 (s, 1 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): 122.9, 124.4, 124.5, 126.1, 128.3, 130.0, 149.8, 154.8.

2,4-Dimethylfuro[3,2-c]quinoline (20)

Yield: 90%.

IR (KBr): 1658, 1589, 1520, 1250 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 14.3$, 103.2, 118.5, 121.8, 122.3, 125.2, 125.7, 128.5, 129.0, 130.0, 130.2, 150.2, 154.4.

Acknowledgment

Thanks to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for their financial support of this work.

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