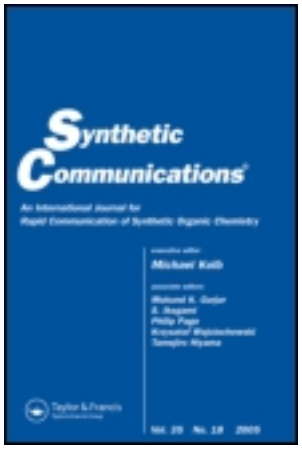

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Synthesis of Some New 3-Substituted Benzofuran Derivatives by Cyclization of Various Phenoxy Acetic Acid Ethyl Esters

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SYNTHESIS OF SOME NEW 3-SUBSTITUTED BENZOFURAN DERIVATIVES BY CYCLIZATION OF VARIOUS PHENOXY ACETIC ACID ETHYL ESTERS

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Six new 2-[3-(1-benzofuran-3-yl)-1H-pyrazol-1-yl] pyridines were synthesized by cyclization of various phenoxy acetic acid ethyl esters using NaOEt in ethanol at room temperature.

Keywords: Benzo[b]furan; phenoxy acetic acid; pyrazole; pyridine

INTRODUCTION

Benzo[b]furans are of great synthetic interest because of their wide distribution in nature and useful biological activities. The various physiological activities associated with benzofuran derivatives led in recent years to the synthesis of a large number of such compounds.[1–7] The benzo[b]furan ring is often incorporated in pharmaceutical agents as a core structural motif and as a result continues to attract extensive synthetic efforts. These compounds have also found use in the synthesis of polycyclic hetrocycles.[8–10]

This article describes the synthesis of 2-{3-[1-benzofuran-3-yl]-1H-pyrazol-1-yl} pyridine. The benzofuran ring-forming reaction has been discussed previously in the chemical literature and clearly involves a number of discrete transformations. A wide variety of benzo[b]furans were synthesized efficiently *via* a CuI-catalyzed ring closure of 2-halo aromatic aldehydes and ketones.[11] Samizu and Ogasawara[12] have reported the synthesis of methyl 3-benzofuranylacetate employing the Heck reaction between 2-iodophenol and 2,5-dihydro-2,5-dimethoxyfuran as a key step. Mooradian[13] has reported the rearrangement of substituted *O*-Aryl oximes to substituted benzofurans. Johnson[14] and coworkers reported the synthesis and screening of a series of 5-(3-pyridylmethyl) benzofuran-2-carboxylic acids as selective thromboxane A_2 (TxA_2) synthase inhibitors. Rao and coworkers reported the synthesis and antifeedant activity of 3-(1-phenyl-1*H*-pyrazol-4-yl)benzofuran-2-carboxylic acids,[15] where they have reported the presence of carboxylic acid at 2-positon of

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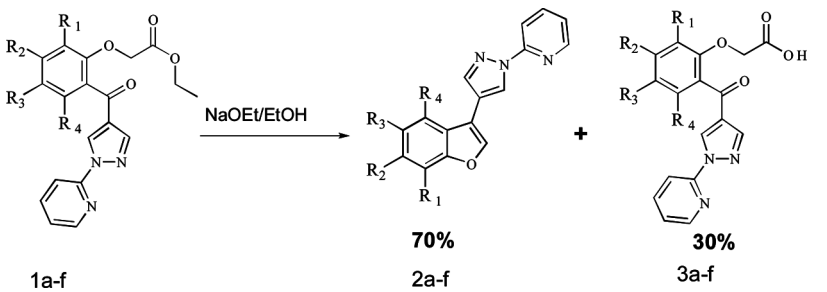
benzofuran using the same protocol as of ours. Herein, we report the absence of carboxylic acid at 2-positon of benzofuran, which we have proved by ^{1}H NMR with D_2O exchange, Mass data as well as the failure in esterification of benzofuran derivatives **2a–f**.

RESULTS AND DISCUSSION

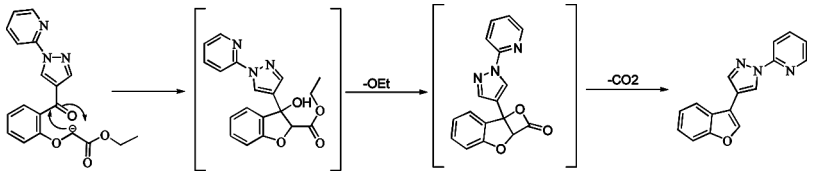
In the present work the required ethyl {2-[(1-(pyridin-2-yl)-1H-pyrazol-4-yl)carbonyl]phenoxy} acetates **1a–f** were prepared from reported literature methods.[15] These phenoxy acetic acid esters **1a–f** on treatment with NaOEt in ethanol at room temperature undergo cyclisation to corresponding benzofuran derivatives (Scheme 1). In earlier study, Rao and colleagues[15] have reported synthesis of 3-(1-phenyl-1*H*-pyrazol-4-yl)benzofuran-2-carboxylic acids having carboxyl functionality at 2-position but in our case we do not find carboxyl functionality, which was confirmed by ^{1}H NMR with D_2O exchange, mass data. The proposed mechanism for the reaction probably proceeds *via* nucleophilic attack of the carbanion to the carbonyl carbon resulting into five membered ring formation followed by the bicyclic β-lactone formation,[16] the β-lactone formed further undergoes decarboxylation[17] to get desired benzofuran derivative (Scheme 2). The structures of these compounds were confirmed by spectral techniques (MS, IR, and ^{1}H NMR). The IR absorption spectra of compounds **2a–f** showed disappearance of absorption band in the range of 1740–1760 cm^{-1} for C=O of ester group and 1630–1660 cm^{-1} for C=O of ketone group of starting material **1a–f** and ^{1}H NMR spectra show a singlet in the range of 8.80–9.00 δ for C_2-H proton of benzofuran **2a–f**, which is not exchangeable with D_2O.

EXPERIMENTAL

Commercial solvents and reagents were used without further purification. The monitoring of reaction and checking of purity of the product were done using pre-coated silica gel plates and visualization using iodine/UV lamp. Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded on Varian



Scheme 1.



Scheme 2. Proposed mechanism.

300 MHz spectrometer in $CDCl_3$ or DMSO as a solvent and TMS as an internal standard. Peak values are shown in δ (ppm). Mass spectra were recorded on a Thermo Finnigan LCQ DECA XP MAX (ION TRAP) LCMSMS mass spectrometer using direct infusion technique. Elemental analysis was performed on a Perkin-Elmer analyzer. Compounds **1a–f** were prepared using previously reported procedures.

General Procedure for Cyclization

The esters **1a–f** (0.01 mol) was added in NaOEt solution (prepared from 0.02 mol of Na and 20 mL of EtOH) and the solution stirred at room temperature

Table 1. Characterization data of various compounds prepared

							Calcd (%) (Found)		
Compound	R_1	R_2	R_3	R_4	Mp (°C)	Yield (%)	C	H	N
2a	H	H	H	H	125	64	73.55 (73.48	4.24 4.10	16.08 15.95)
2b	H	H	Br	H	124	68	56.49 (56.24	2.96 2.78	12.35 12.10)
2c	H	CH_3	H	H	71	64	74.17 (74.15	4.76 4.68	15.26 15.20)
2d	H	CH_3	Cl	H	181	66	65.92 (65.88	3.90 3.85	13.57 13.46)
2e	H	H	C_2H_5	H	137	65	74.72 (74.50	5.23 5.04	14.52 14.25)
2f	H	H	CH_3	H	233	66	74.17 (74.00	4.76 4.70	15.26 15.10)
3a	H	H	H	H	107	24	63.15 (63.04	4.05 3.96	13.00 12.90)
3b	H	H	Br	H	114	28	50.77 (50.67	3.01 2.94	10.45 10.28)
3c	H	CH_3	H	H	97	22	64.09 (64.00	4.48 4.38	12.46 12.34)
3d	H	CH_3	Cl	H	121	26	58.15 (58.04	3.80 3.72	11.30 11.18)
3e	H	H	C_2H_5	H	110	20	64.95 (64.80	4.88 4.76	11.96 11.80)
3f	H	H	CH_3	H	142	18	64.09 (64.00	4.48 4.30	12.46 12.32)

Table 2. Spectral data of compounds **2a–f**

Benzofuran derivative	Spectral data
2a	IR (KBr, cm^{-1}): 3138, 2890, 1588, 1478, 1466, 1088, 778. ^1H NMR ($CDCl_3$): δ 7.20–7.30 (m, 1H), 7.30–7.44 (m, 2H), 7.55 (d, 1H, J = 7.2 Hz), 7.80–7.90 (m, 3H), 8.00–8.08 (m, 2H), 8.46 (d, 1H, J = 3.3 Hz), 8.91 (s, 1H). MS ($M^+ + 1$): 262.34.
2b	IR (KBr, cm^{-1}): 3132, 2921, 1594, 1478, 1456, 1098, 773. ^1H NMR ($CDCl_3$): δ 7.20–7.30 (m, 1H), 7.40–7.52 (m, 2H), 7.82–8.04 (m, 5H), 8.47 (s, 1H), 8.87 (s, 1H). MS ($M^+ + 1$): 340.66, ($M^+ + 3$):342.63.
2c	IR (KBr, cm^{-1}): 3118, 2902, 1598, 1480, 1454, 1086, 786. ^1H NMR($CDCl_3$): δ 2.51 (s, 3H), 7.17 (d, 1H, *J* = 7.2 Hz), 7.20–7.34 (m, 1H), 7.36 (s, 1H), 7.72 (d, 1H, *J* = 8.1 Hz), 7.80 (s, 1H), 7.86 δ (t, 1H, *J* = 8.4 Hz), 7.98–8.08 (m, 2H), 8.46 (d, 1H, *J* = 3.6 Hz), 8.89 (s, 1H). MS ($M^+ + 1$): 276.61.
2d	IR (KBr, cm^{-1}): 3160, 2944, 1600, 1490, 1468, 1110, 790. ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H), 7.18–7.34 (m, 1H), 7.41 (s, 1H), 7.76–7.84 (m, 2H), 7.86 (t, 1H, *J* = 7.2 Hz), 7.96–8.10 (m, 2H), 8.47 (d, 1H, *J* = 3.6 Hz), 8.87 (s, 1H). MS ($M^+ + 1$): 310.55, ($M^+ + 3$):312.77.
2e	IR (KBr, cm^{-1}): 3142, 2942, 1590, 1488, 1466, 1090, 794. ^1H NMR ($CDCl_3$): δ 1.32 (t, 3H, *J* = 7.8 Hz), 2.81 (q, 2H, *J* = 7.5 Hz), 7.18–7.36 (m, 2H), 7.46 (d, 1H, *J* = 8.4 Hz), 7.62 (s, 1H), 7.78–7.94 (m, 3H), 8.00–8.08 (m, 2H), 8.47 (d, 1H, *J* = 3.3 Hz), 8.89 (s, 1H). MS ($M^+ + 1$): 290.44.
2f	IR (KBr, cm^{-1}): 3154, 2932, 1584, 1474, 1460, 1102, 760. ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H), 7.16–7.32 (m, 2H), 7.43 (d, 1H, *J* = 8.4 Hz), 7.62 (s, 1H), 7.78–7.94 (m, 2H), 7.98–8.08 (m, 2H), 8.48 (s, 1H), 8.89 (s, 1H). MS ($M^+ + 1$): 276.94.

Table 3. Spectral data of compounds **3a–g**

Acid derivative	Spectral data
3a	IR (KBr, cm^{-1}): 3168, 3065, 1744, 1723, 1629, 1596, 1547, 1460, 1217, 1167, 785. ^1H NMR ($CDCl_3$): δ 4.83 (s, 2H), 7.11 (d, 1H, *J* = 8.1 Hz), 7.18–7.32 (m, 2H), 7.68 (d, 1H, *J* = 7.5 Hz), 7.58 (t, 1H, *J* = 7.5 Hz), 7.85 (t, 1H, *J* = 7.2 Hz), 8.02 (d, 1H, *J* = 7.8 Hz), 8.23 (s, 1H), 8.44 (d, 1H, *J* = 3.6 Hz), 9.02 δ (s, 1H).
3b	IR (KBr, cm^{-1}): 3224, 3125, 1756, 1728, 1609, 1574, 1522, 1432, 1209, 1142, 754. ^1H NMR ($CDCl_3$): δ 4.18 (brs, 1H, due to OH), 4.78 (s, 2H), 6.96–7.02 (m, 1H), 7.40–7.50 (m, 1H), 7.60–8.10 (m, 3H), 8.21 (s, 1H), 8.44–8.52 (m, 1H), 8.88 (s, 1H), 9.03 (s, 1H).
3c	IR (KBr, cm^{-1}): 3162, 3076, 1752, 1732, 1634, 1588, 1547, 1460, 1167, 782. ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 4.83 (s, 2H), 6.93 (s, 1H), 7.01 (d, 1H, *J* = 8.1 Hz), 7.20–7.34 (m, 1H), 7.59 (d, 1H, *J* = 7.8 Hz), 7.89 (t, 1H, *J* = 6.9 Hz), 8.04 (d, 1H, *J* = 8.1 Hz), 8.43 (d, 1H, *J* = 3.6 Hz), 9.02 (s, 1H).
3d	IR (KBr, cm^{-1}): 3164, 3072, 1748, 1718, 1622, 1586, 1534, 1220, 1160, 764. ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H), 4.12 (brs, 1H, due to OH), 4.77 (s, 2H), 6.96 (s, 1H), 7.20–7.34 (m, 1H), 7.60 (d, 1H), 7.87 (t, 1H, *J* = 7.2 Hz), 8.02 (d, 1H, *J* = 8.4 Hz), 8.20 (s, 1H), 8.43 (s, 1H), 9.02 (s, 1H). MS (M-1): 370.14.
3e	IR (KBr, cm^{-1}): 3122, 3021, 1746, 1713, 1642, 1596, 1544, 1444, 1217, 765. ^1H NMR ($CDCl_3$): δ 4.83 (s, 2H), 7.11 (d, 1H, *J* = 8.1 Hz), 7.18–7.32 (m, 2H), 7.68 (d, 1H, *J* = 7.5 Hz), 7.58 (t, 1H, *J* = 7.5 Hz), 7.85 (t, 1H, *J* = 7.2 Hz), 8.02 (d, 1H, *J* = 7.8 Hz), 8.23 (s, 1H), 8.44 (d, 1H, *J* = 3.6 Hz), 9.02 (s, 1H).
3f	IR (KBr, cm^{-1}): 3088, 2978, 1734, 1712, 1589, 1544, 1430, 1207, 1147, 778. ^1H NMR ($CDCl_3$): δ 2.36 (m, 3H), 6.98 (d, 1H, *J* = 8.4 Hz), 7.20–7.40 (m, 2H), 7.71 (s, 1H), 7.90 (t, 1H, *J* = 6.6 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 8.21 (s, 1H), 8.48 (s, 1H), 9.12 (s, 1H).

for 18 h, diluted with water (20 mL) and neutralized with acetic acid. The aqueous layer was extracted with ethyl acetate and washed with water, brine and dried over anhydrous sodium sulphate and purified through column chromatography to yield desired benzofuran derivative **2a–f** as off-white solid and a part of starting material get hydrolysied to phenoxy acetic acid **3a–f** as side product, was also isolated. Compounds synthesized by the above procedure are listed in Table 1 and their characterization is given in Tables 2 and 3.

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