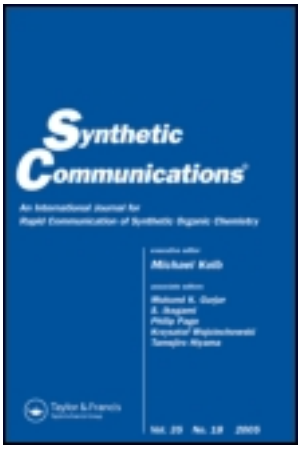

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 24 Feb 2007.

To cite this article: Vijai N. Pathak , Ragini Gupta , Ranjana Tiwari , Rekha Gupta , Vineeta Sareen & Bindu Varshney (2007): Synthesis of Some Novel 2,3,4,8,9-Pentahydro-7-(4-haloaryl)-pyrazolo[5,1-e]benzo[1,5]oxazocines and 2,3(erythro), 7,8-Tetrahydro-2-aryl-3-(4-fluoro-3-methylbenzoyl)-6-(4-haloaryl)pyrazolo[5,1-d] Benzo[1,4]oxazepines via Solid-Liquid PTC, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:6, 977-984

To link to this article: http://dx.doi.org/10.1080/00397910601163927

Synthetic Communications®, 37: 977–984, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910601163927

Synthesis of Some Novel 2,3,4,8,9-Pentahydro-7-(4-haloaryl)-pyrazolo[5,1-e]benzo[1,5]oxazocines and 2,3(*erythro*), 7,8-Tetrahydro-2-aryl-3-(4-fluoro-3-methylbenzoyl)-6-(4-haloaryl)pyrazolo[5,1-d] Benzo[1,4]oxazepines via Solid–Liquid PTC

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Abstract: In this communication, a simple and straightforward procedure for the heterocyclization of 1H-4,5-dihydro-3-(4-haloaryl)-5-substituted phenylpyrazoles (**4**) with 1-bromo-3-chloropropane and 2,3-dibromo-1-(4-fluoro-3-methylphenyl)-3-phenylpropanone affording 2,3,4,8,9-pentahydro-7-(4-haloaryl)pyrazolo[5,1-e]benzo[1,5] oxazocines **5** and regioselective synthesis of 2,3(*erythro*),7,8-tetrahydro-2-aryl-3-(4-fluoro-3-methylbenzoyl)-6-(4-halophenyl)pyrazolo[5,1-d]benzo[1,4]oxazepines **6,** respectively, via solid–liquid PTC is reported. All the synthesized

Received August 18, 2006
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compounds have been characterized on the basis of their spectral studies (IR, PMR, and MS) and analytical data.

Keywords: 1,4-benzoxazepines, 1,5-benzoxazocines, dihaloalkane, heterocyclization, pyrazoles, regioselective synthesis, solid–liquid phase-transfer catalysis

INTRODUCTION

Benzo-fused seven-membered and eight-membered ring heterocycles have gained recognition in the therapeutic armanentarium because they serve as important central nervous system (CNS) and cardiovascular agents. Nefopam, a 1H-2,5-benzoxazocine is a nonsedative nonnarcotic analgesic.[1] Basil et al.[2] have reported the synthesis of a series of 1,5-benzoxazocine derivatives and have found that 3,4-dihydro-3-hydroxy-6-methyl-1,5-benzoxazocine possessed high sympathetic β–blocker activity. Diazepam, a 2H-1,4-benzodiazepin-2-one is a significant erythro-anxiety drug (tranquilizer).[3–5] More recently, it has shown potential as an erythroepileptic drug.[6] Dilitiazem, a 1,5-benzothiazepinone is a well-known calcium-channel antagonist used for the treatment of hypertension.[7,8] 1,5-Benzoxazepine derivatives have been reported to show potent erythroconvulsant activity by Bajaj et al.[9] 4,1-Benzoxazepine derivatives exhibited squalene synthase inhibitory activity,[10] and **JL 13**, a pyridobenzoxazepine, possessed atypical erythropsychotic activity.[11,12]

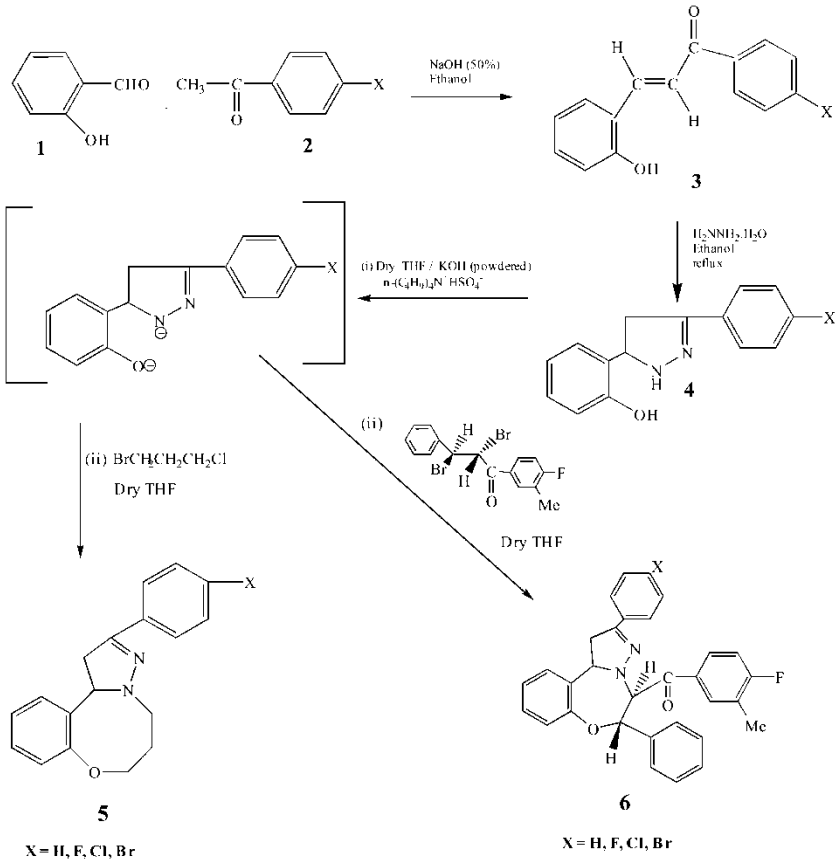
In light of these observations and in continuation to our previous work on bioactive fluorinated/nonfluorinated heterocycles and phase-transfer catalysis (PTC),[13] we thought it worthwhile to synthesize derivatives of these biologically useful heterocycles by using a simple, convenient, and mild phase-transfer-catalyzed heterocyclization approach leading to the synthesis of 2,3,4,8,9-pentahydro-7-(4-haloaryl)pyrazolo[5,1-e]benzo [1,5]oxazocines **5(a–d)** and regioselective synthesis of 2,3(*erythro*),7,8-tetrahydro-2-aryl-3-(4-fluoro-3-methylbenzoyl)-6-(4-haloaryl)pyrazolo[5,1-d]benzo[1,4]oxazepines **6(a–d)** via solid–liquid PTC (Scheme 1).

RESULTS AND DISCUSSION

Synthesis

Various 1,3-diarylprop-2-enones **3(a–d)** were prepared by condensation of salicylaldehyde and aryl methyl ketones in the presence of 50% NaOH solution and characterized as *trans* 1,3-diaryl-2-propenones on the basis of their IR and proton magnetic resonance (PMR) spectral data, which were consistent with earlier results.[14,15]

The appropriate 1,3-diarylprop-2-enone (**3**) was treated with hydrazine hydrate (80%) in ethanol to afford the desired 1H-4,5-dihydro-3-(4-haloaryl)-5-(2-hydroxyphenyl)pyrazole **4(a–d)**. The PMR spectra of these



Scheme 1.

compounds **4** exhibited a characteristic ABX pattern for methylene group (a prochiral -CH_2 group, which contains two nonequivalent protons). The resonance signals at δ 2.8–3.2 (double doublet due to α-C*H* of CH_2 group), 3.5–4.0 (double doublet due to β-C*H* of CH_2 group), and 5.5–5.8 ppm (double doublet due to methine group -C*H*). These compounds also exhibited D_2O exchangeable resonance signals at δ 11.0 and 8.82 ppm due to N*H* and O*H* protons, respectively. The aromatic resonance signal appears as a multiplet at δ 6.94–8.32 ppm.

The reaction of 1H-4,5-dihydro-3-(4-haloaryl)-5-(2-hydroxyphenyl)pyrazoles **4(a–d)** with 1-bromo-3-chloropropane in the presence of tetra-*n*-butylammonium hydrogen sulphate in dry THF and powdered potassium hydroxide (KOH) gave **5(a–d)**. In their PMR spectra, two triplets at δ 4.25 and 4.50 ppm corresponding to -N-CH_2- and -O-CH_2- appeared. Further confirmation for their formation was obtained from mass spectra.

Treatment of 2,3-dibromo-1-(4-fluoro-3-methylphenyl)-3-phenylpropanone with the dianion of appropriate 1H-4,5-dihydro-3-(4-haloaryl)-5-(2-hydroxyphenyl)-pyrazoles **4(a–d)** (generated by solid–liquid PTC as described earlier) gave **6(a–d)**. In the PMR spectra, appearance of two double doublets at δ 4.10 and 4.50 ppm ($J = 10$ Hz) corresponds to -N-C*H* and -O-C*H* (erythro). Further evidence is obtained by mass spectra where the molecular ion peaks M^+ at m/z 476 (33.2%) for the compound **6a** and at m/z 510 (9.2%) for the compound **6c** are observed (Table 1).

EXPERIMENTAL

Melting points were recorded in open glass capillaries and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded using Perkin-Elmer model 557 in KBr pellets and Nicholet Magna model-750 spectrophotometer in KBr pellets at Central Drug Research Institute (CDRI), Lucknow, and Department of Chemistry, University of Rajasthan, Jaipur. PMR spectra were recorded on Jeol FX-90 Q at 89.55 Hz at Department of Chemistry, University of Rajasthan, Jaipur, and on Bruker spectrophotometer (200 MHz) at CDRI, Lucknow, in $CDCl_3$ solution with TMS as an internal standard (chemical shift in δ ppm). Mass spectra were recorded on Kratos-30 and 50 mass spectrometer at CDRI, Lucknow. 2,3-Dibromo-1-(4-fluoro-3-methylphenyl)-3-phenylpropanone was synthesized by the literature method.[16] All compounds are homogeneous on thin-layer chromatography (TLC) in various solvent systems.

Synthesis of 1-(4-Fluorophenyl)-3-(2-hydroxyphenyl)-prop-2-enone (3d)

A mixture of salicyaldehyde (**1**) (1.22 g, 10 mmol) and 4-fluoroacetophenone (**2**) (1.38 g, 10 mmol) in EtOH (50 mL) was heated in a water bath for 15 min, then 50% aqueous NaOH solution (10 mL) was added. The resulting thick mass was stirred for 3 h, then left overnight at room temperature and neutralized by pouring into ice-cold 2 N HCl (100 mL). The solid was filtered, dried, and recrystallized from ethanol to afford (**3d**).[17] Yield: 2.38 g (98%), mp: 150°C. Compounds **3(a–c)** were prepared similarly.

Synthesis of 1H-4,5-Dihydro-3-(4-fluorophenyl)-5-(2-hydroxyphenyl)pyrazole (4d)

A mixture of 1-(4-fluorophenyl)-3-(2-hydroxyphenyl)-prop-2-enone (**3d**) (0.968 g, 4 mmol) and hydrazine hydrate (5 mL, 80%) in ethanol (50 mL) was refluxed in a water bath for 5 h, concentrated, and poured over crushed ice. The solid was filtered and recrystallized from ethanol to yield (**4d**).

Table 1. Spectroscopic data of 2,3,4,8,9-pentahydro-7-(4-haloaryl)pyrazolo[5,1-e]benzo[1,5] oxazocines (**5**) and 2,3(*erythro*),7,8-tetrahydro-2-aryl-3-(4-fluoro-3-methylbenzoyl)-6-(4-haloaryl)pyrazolo[5,1-d]benzo[1,4]oxazepines (**6**)

Compound. no.	IR ν_{max} (cm^{-1}) (KBr)	^1H NMR δ (ppm) ($CDCl_3$)	MS: (m/z)
5a	3040–3080 m (aromatic C-C str.), 2870–2990 m (aliphatic C-C str.), 1610–1600vs (-C═N str.), 1580–1575 s (aromatic -C═C str.), 1500 m, 1450 m, 1300 w, 1200–1000vs (-C-O-C str.)	7.3–7.5 (m, Ar-H, 9H), 5.5–5.8 (dd, -CH, 1H), 4.50 (t, $^3J = 7.0$ Hz, -O-CH_2, 2H), 4.25 (t, $^3J = 6.8$ Hz, -N-CH_2, 2H), 3.5–4.0 (dd, -CH_α-CH_β, 1H), 2.8–3.2 (dd, -CH_α-CH_β, 1H), 2.0 (m, -CH_2, 2H)	—
5b	3050–3080 m (aromatic C-C str.), 2860–2990 m (C-C str.), 1611–1602vs (C═N str.), 1587–1582 s (aromatic -C═C str.), 1200–1000 s (-C-O-C str.), 530 m (-C-Br str.)	7.3–7.5 (m, Ar-H, 8H), 5.6–5.8 (dd, -CH, 1H), 4.53 (t, $^3J = 7.1$ Hz, -O-CH_2, 2H), 4.26 (t, -N-CH_2, 2H), 3.6–4.0 (dd, -CH_α-CH_β, 1H), 2.9–3.1 (dd, -CH_α-CH_β, 1H), 2.0 (m, -CH_2, 2H)	357 (M + 1, 100%) 356 (M^+, 23.2%)
5c	3040–3070 m (aromatic C-C str.), 2860–2990 m (aliphatic C-C str.), 1613–1605vs (-C═N str.), 1594–1588 s (aromatic -C═C str.), 1200–1000vs (-C-O-C str.), 735 w (-C-Cl str.)	7.3–7.5 (m, Ar-H, 8H), 5.5–5.7 (dd, -CH, 1H), 4.54 (t, $^3J = 7.0$ Hz, -O-CH_2, 2H), 4.28 (t, -N-CH_2, 2H), 3.8–4.0 (dd, -CH_α-CH_β, 1H), 2.8–3.0 (dd, -CH_α-CH_β, 1H), 2.1 (m, -CH_2, 2H)	312 (M^+, 100%)
5d	3050–3070 m (aromatic C-C str.), 2860–2990 m (aliphatic C-C str.), 1616–1609vs (-C═N str.), 1601–1596s (aromatic -C═C str.), 1200–1000vs (-C-O-C str.), 859 m (-C-F str.)	7.5–7.7 (m, Ar-H, 8H), 5.5–5.8 (dd, -CH, 1H), 4.54 (t, $^3J = 7.0$ Hz, -O-CH_2, 2H), 4.29 (t, -N-CH_2, 2H), 3.9–4.1 (dd, -CH_α-CH_β, 1H), 2.9–3.2 (dd,-CH_α-CH_β, 1H), 2.2 (m, -CH_2, 2H)	296 (M^+, 100%)
6a	3040–3070 m (aromatic C-C str.), 2850–2990 m (aliphatic C—C str.), 1660vs (-C═O str.), 1616–1609vs (-C═N str.), 1601–1596vs (aromatic -C═C str.), 1200-1010vs (-C-O-C str.), 1585–1575 m (aromatic str.), 1110 w, 850 m (-C-F str.), 625 m	7.5–7.8 (m, Ar-H, 17H), 4.50 (dd, $J = 10$ Hz, -O-CH, 1H), 4.10 (dd, $J = 10$ Hz, -N-CH, 1H), 5.5–5.8 (dd, -CH, 1H), 3.9–4.1 (dd, -CH_α-CH_β, 1H), 2.9–3.2 (dd, -CH_α-CH_β, 1H), 2.2 (m, -CH_2, 2H), 2.1 (s, CH_3, 3H)	476 (M^+, 33.2%), 325 ($C_{22}H_{17}N_2O$ (100%)

(*continued*)

Table 1. Continued

Compound. no.	IR ν_{max} (cm^{-1}) (KBr)	^1H NMR δ (ppm) ($CDCl_3$)	MS: (m/z)
6b	3045–3070 m (aromatic C-C str.), 2840–2980 m (aliphatic C-C str.), 1665vs (-C=O str.), 1616–1609vs (-C=N str.), 1601–1596vs (aromatic -C=C str.), 1200–1000vs (-C-O-C str.), 1580–1575 m (aromatic str.), 1100 w, 810 m, 780 m, 625 m (-C-Br str.)	7.2–7.8 (m, Ar-H, 16H), 4.52 (dd, $J = 10$ Hz, -O-CH, 1H), 4.15 (dd, $J = 10$ Hz, -N-CH, 1H), 5.43–5.82 (dd, -CH, 1H), 3.94–4.15 (dd, $-CH_\alpha$-CH_β, 1H), 2.91–3.2 (dd, $-CH_\alpha$ $-CH_\beta$, 1H), 2.2 (m, $-CH_2$, 2H), 2.0 (s, CH_3, 3H)	—
6c	3040–3070 m (aromatic C-C str.), 2850–2990 m (aliphatic C-C str.), 1660vs (-C=O str.), 1616–1609vs (-C=N str.), 1601–1596vs (aromatic -C=C str.), 1210–1000vs (-C-O-C str.), 1580–1575 m (aromatic str.), 1105 w, 615 m (-C-Cl str.)	7.5–7.8 (m, Ar-H, 16H), 4.54 (dd, $J = 10$ Hz, -O-CH, 1H), 4.18 (dd, $J = 10$ Hz, -N-CH, 1H), 5.45–5.81 (dd, -CH, 1H), 3.89–4.1 (dd, $-CH_\alpha$-CH_β, 1H), 2.9–3.24 (dd, $-CH_\alpha$ $-CH_\beta$, 1H), 2.2 (m, $-CH_2$, 2H), 1.94 (s, CH_3, 3H)	510 (M^+, 9.2%)
6d	3040–3070 m (aromatic C-C str.), 2850–2990 m (aliphatic C-C str.), 1670vs (-C=O str.), 1616–1600vs (-C=N str.), 1600–1595vs (aromatic -C=C str.), 1200–1010vs (-C-O-C str.), 1580–1575 m (aromatic str.), 1145s (-C-F, str.)	7.3–7.8 (m, Ar-H, 16H), 4.51 (dd, $J = 10.1$ Hz, -O-CH, 1H), 4.12 (dd, $J = 10.1$ Hz, -N-CH, 1H), 5.6–5.8 (dd, -CH, 1H), 3.9–4.1 (dd, $-CH_\alpha$-CH_β, 1H), 2.9–3.15 (dd, $-CH_\alpha$-CH_β, 1H), 2.18 (m, $-CH_2$, 2H), 2.1 (s, CH_3, 3H)	—

Yield: 1.0 g (98%), mp: 74°C. Other compounds **4(a–c)** were prepared similarly.

Synthesis of 2,3,4,8,9-Pentahydro-7-(4-fluorophenyl)pyrazolo[5,1-e]benzo[1,5] oxazocine (5d)

Compound (**4d**) (0.51 g, 2 mmol) and tetra-*n*-butylammonium hydrogen sulphate (0.68 g, 2 mmol) were dissolved in dry THF (20 mL). Then powdered KOH (20 g) followed by 1-bromo-3-chloropropane (0.30 mL, 2 mmol) in THF (20 mL) were added. The resultant reaction mixture was stirred for 8 h. THF was removed, and the resultant residue dissolved into

Table 2. Physical data of compounds **3**–**6**

Compound no.	Substituent in aryl moiety[a] (X)	mp[b] (°C)	Yield[c] (%)
3a	H	124	80
3b	4-Br	136	96
3c	4-Cl	140	98
3d	4-F	151	98
4a	H	173	82
4b	4-Br	150	92
4c	4-Cl	170	95
4d	4-F	76	97
5a	H	102	52
5b	4-Br	124	57
5c	4-Cl	144	58
5d	4-F	150	56
6a	H	178	56
6b	4-Br	150	59
6c	4-Cl	120	54
6d	4-F	188	57

[a]Satisfactory C, H and N analyses were obtained.
[b]All compounds were recrystallized form ethanol.
[c]Yield refers to purified products obtained after column chromatography.

chloroform. It was washed with water, dried over anhydrous sodium sulphate, and concentrated; light pertroleum was added, and the solid was filtered. Recrystallization from ethanol afforded **(5d)**. Yield: 0.33 g (55.76%), mp: 150°C. Other compounds were prepared by this method (Table 2).

Synthesis of 2,3(Erythro),7,8-tetrahydro-2-aryl-3-(4-fluoro-3-methylbenzoyl)-6-(4-fluorophenyl)pyrazolo[5,1-d] benzo[1,4]oxazepine (6d)

Compound **6d** was prepared as described earlier. Yield 56.7%; mp 188°C.

ACKNOWLEDGMENTS

Authors are thankful to University Grants Commission (UGC), New Delhi, for financial assistance. Authors also record their sincere thanks to V. J. Ram, emeritus scientist, Medicinal Chemistry Division, Central Drug Research Institute (CDRI), Lucknow, and K. P. Madhusudanan, deputy director and

head, sophisticated analytical instrument facility (SAIF), CDRI, Lucknow, for spectral and analytical analyses.

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