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Synthesis of New Furan Compounds: A Study towards Pyrrole Ring

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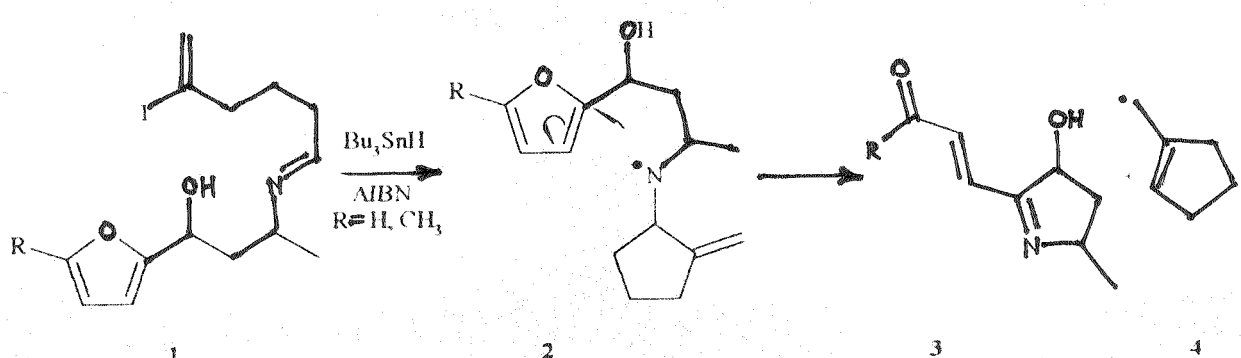
Synthesis towards the precursor **1** for radicalic reaction has been studied. 3-Methyl-5-(5-methylfuran-2-yl)-4,5-dihydro-isoxazole, (**7**) was obtained from vinyl furan. 2-(4-Iodo-pent-4-enyl)-4-methyl-6-(5-methyl-furan-2-yl)-[1,3]oxazinane (**13**) was generated using the amino alcohol **8** and corresponding aldehyde (**11**). Selective protection on the amino alcohol was achieved. Steric hindrance of amino group behaved obstructive to a condensation reaction.

Key Words: Synthesis, Furan, Intra-, Intermolecular, Hetero, Radicalic cyclization.

INTRODUCTION

Synthesis of nitrogen heterocycles through radical reaction has been one of the most attractive fields for organic chemists. The most radical cyclizations proceed by 5-*exo-trig* regio-selectivity and provide the main protocols used in heterocyclic synthesis. Therefore, the majority of nitrogen heterocycles synthesized by radical cyclizations have five-membered rings[1]. Parsons and his coworkers[2] have discovered the addition of alkenyl radicals to furans: the intermediate process gives carbocyclic rings over fragmentation. This radical reaction is performed by tri-*n*-butyltin hydride in the presence of azobis-*iso*butyronitrile (AIBN)[3]. In the present communication, an attempt has been made to improve this chemistry for the synthesis of pyrrole ring by using alkenyl iodide **1** (**Scheme-1**).



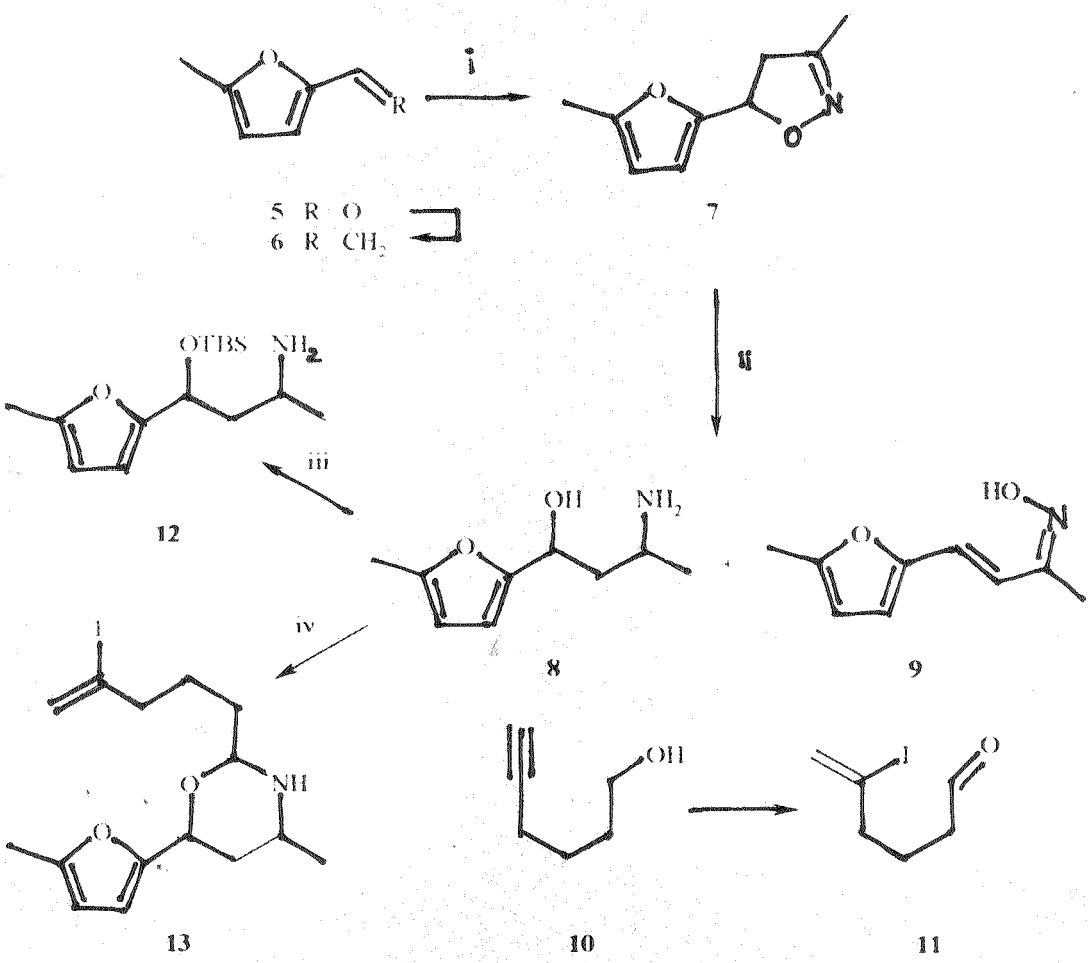
1 2 3 4

Scheme-1. Cycloadition/fragmentation progress for pyrrole ring

The alkenyl radical would undergo first 5-*exo* trig additions to give aminyl radical **2**, which would then be able to achieve second 5-*exo* trig additions to furan. The resulting spiro-cyclic compound would have fragmented to give highly substituted pyrrole rings **3**.

RESULTS AND DISCUSSION

Synthetic route towards the alkenyl iodide (**1**) is outlined in **Scheme-2**; Wittig reaction with 5-methylfurfural (**5**) resulted into vinylfuran (**6**); a facile synthesis of isoxazole (**7**) from vinylfuran (**6**) was achieved by using phenyl isocyanate and nitroethane[3] at 0°C. Reduction of isoxazole (**7**) was problematic, due to being hydroxyl group next to hetero-aromatic ring, producing oxime (**9**) as a major product beside amino alcohol (**8**) in 40% yield[4]. Iodoalkenal (**11**) was previously synthesized from 5-hexyn-1-ol, which was initially reduced to iodoalkenol, followed by Dess-Martin periodinane oxidation to give the desired aldehyde (**11**)[5, 6]. Treatment of amino alcohol (**8**) with iodoalkenal (**11**) in dichloromethane at room temperature provided the oxazinane (**13**) in 85% yield, instead of expected precursor **1**[7]. Therefore, alcohol side of **8** was protected to convert its silyl-ether by using standard method[8].



Scheme-2

(i) PhNCO, $EtNO_2$, Et_3N, DCM, 0°C, 98%; (ii) $LiAlH_4$, –10°C, Et_2O, 40%; (iii) TBDMSOTf, 2,6-lutidine, DCM, –78°C, 61%; (iv) DCM, mol. sieves, **11**, 85%.

The amine (**12**) was then reacted with iodoalkene (**11**) under several conditions such as; toluene, Dean-Stark; dichloromethane, 4 Å, molecular sieves, room temperature; DCM : MeOH (4 : 1), room temperature reflux, 4 Å mol. sieves powder; C_6D_6, 4 Å mol. sieves powder. Hitherto, we have been unable to tune the reaction conditions to furnish the imine **1** in more than trace quantities. However, we synthesized new isoxazole and oxazinane in addition to 1,3-aminoalcohol **8**, that has potential application on furan's chemistry. Our results will be published on this area in due course.

EXPERIMENTAL

Solvents and reagents were freshly distilled as follows: tetrahyrdofuran (THF) and diethyl ether were distilled from sodium/benzophenone; toluene was distilled from calcium hydride. Petroleum-ether (40–60°C) (PE) and hexane were distilled before use. Reactions were monitored by thin layer chromatography (TLC) using pre-coated silica plates (Macharey Nagel sil G UV_{254}). Compounds were visualized using ultra-violet fluorescence, alkaline potassium permanagate solution or acidic cerium(IV) sulphate solution. Column chromatography was carried out by Macharey Nagel Kieselgel 60 (230–240 mesh). ^1H NMR spectra were recorded on a Bruker 300 MHz DPX 300 spectrometer. The chemical shifts are quoted in ppm, as δ values downfield of tetramethylsilane (TMS) or relative to the residual solvent resonance. Infrared spectra were recorded on a Perkin-Elmer 1720 spectrophotometer; Solid samples were recorded using potassium bromide discs and liquid samples were recorded as thin films. Electron ionization mass spectra (EI, 70 eV) were obtained on a Fisions VG Auto spec mass spectrometer. Melting points are measured on Electrothermal 9100 15 V, *ca.* 56/60 Hz, 45 W.

3-Methyl-5-(5-methylfuran-2-yl)-4,5-dihydroisoxazole (7)

5-Methyl-2-viniylfuran, **6** (1.63 g, 15.1 mmol) and 10 drops of triethylamine in DCM (20 mL) were added to an ice-cold solution of phenyl isocyanate (13.4 g, 112.5 mmol) and nitroethane (8.4 g, 112.5 mmol) in DCM (250 mL). The reaction mixture was stirred for 3 h at room temperature and the yellow suspension was filtered off. The filtrate was evaporated and the residue was subjected to flash column chromatography to afford the title compound as pale yellow oil, with (2.45 g) 98% yield. TLC, R_f: 0.3 (PE : diethyl ether (7 : 3)). IR ν_{max}/cm^{-1}: 2925 (s), 1613 (m), 1163 (s). δ_H ($CDCl_3$, 300 MHz): 6.1 (d, J 3.0 Hz, 1H), 5.75 (d, J 3.0 Hz, 1H), 5.3 (t, J 9.3 Hz, 1H), 3.0 (m, 2H), 2.15 (s, 3H), 1.85 (s, 3H). δ_C (75.5 MHz, $CDCl_3$): 165.0, 155.5, 153.4, 109.9, 106.7, 75.3, 42.6, 14.0, 13.6. m/z (GC-MS): ($C_9H_{11}NO_2$): 165 [M^+, 17%], 149 [M^+-CH_3, 20%]. M.w.: (Found: 165.077; requires: 165.0789).

3-Amino-1-(5-methylfuran-2-yl)butan-1-ol (8)

Lithium aluminium hydride in THF (1 M) (9 mL, 9 mmol) was added dropwise to a stirred solution of 3-methyl-5-(5-methyl-furan-2-yl)-4,5-dihydro-isoxazole **7**, (0.5 g, 3 mmol) in diethyl ether (15 mL) at −10°C. The reaction mixture was stirred for 2 h at ambient temperature. Rochelle's salt was added carefully; the

solid was filtered off and washed with ether. Combined extracts were dried over Na_2SO_4, then filtered off and evaporated. The residue was subjected to flash column chromatography to afford the title compound as orange oil in (0.2 g) 40% yield. TLC, R_f: 0.13 (EtOAc : DCM : MeOH (8 : 1 : 1)). IR ν_{max}/cm^{-1}: 3353 (brd), 2923 (s), 1567 (s), 1101 (s), 1020 (m). δ_H ($CDCl_3$, 300 MHz): 6.1 (d, J 3.0 Hz, 1H), 5.85 (d, J 3.0 Hz, 1H), 4.85 (dd, J_1 10 Hz, J_2 3 Hz, 1H), 3.2 (br, 4H, NH_2, OH, 1H), 2.25 (s, 3H), 1.82 (m, 2H), 1.1 (d, J 6.5 Hz, 3H). δ_C (75.5 MHz, $CDCl_3$): 155.6, 151.6, 106.3, 106.2, 68.9, 48.5, 42.9, 27.2, 13.9. m/z (GC-MS): ($C_{9H_{11}}NO_2$): 169 [M^+, 40%] , 152 [M^+-OH, 50%], 137 [M^+-(OH + NH_2), 100%]. M.w.: (Found: 169.1094; requires: 169.1102).

4-(5-Methylfuran-2-yl)but-3-en-2-oxime (9)

50% yield. δ_H ($CDCl_3$, 300 MHz): 7.25 (d, J 16.4 Hz, 1H), 6.25 (d, J 16.4, 1H), 6.3 (d, J 3.0 Hz, 1H), 5.9 (d, J 3.0 Hz, 1H), 2.25 (s, 3H), 1.90 (s, 3H). m/z (GC-MS): ($C_9H_{11}NO_2$): 166 [M^+, 20%], 164 [M^+-2H, 95%], 148 [90%].

3-(*t*-Butyldimethylsilyloxy)-1-methyl-3-(5-methylfuran-2-yl)propylamine (12)

2,6-Lutidine (0.256 mL, 2.2 mmol) was added to stirred solution of 3-amino-1-(5-methylfuran-2-yl)butan-1-ol, **8** (0.19 g, 1.1 mmol) in dry DCM (10 mL) and stirred for 10 min. *t*-Butyl-dimethylsilyl trifluoromethane sulphonate (0.29 g, 1.1 mmol) was then added dropwise and stirred for 1 h at –78°C. The reaction mixture was stirred further for 2 h at room temperature before being quenched with water. The mixture was then extracted with diethyl ether 3 × 20 mL, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to flash column chromatography to afford the titled compound as brown oil with (0.19 g) 61% yield. TLC, R_f: 0.4 (EtOAc : DMC : MeOH (7 : 2 : 1)). IR ν_{max}/cm^{-1}: 3363 and 3353 (sd), 2929 (s), 1741 (s), 1082. δ_H ($CDCl_3$, 300 MHz): 6.0 (d, J 3.0 Hz, 1H), 5.58 (d, J 3.0 Hz, 1H), 4.7 (t, J 8.5 Hz, 1H), 2.8 (br, 2H, NH_2), 2.2 (s, 3H), 2.0 (m, 1H), 1.8 (m, 2H), 1.1 (d, J 6.3 Hz, 3H), 0.9 (s, 9H), 0.0 (s, 6H). δ_C (75.5 MHz, $CDCl_3$): 154.9, 151.5, 107.3, 106.3, 67.5, 46.1, 45.2, 26.1, 23.8, 18.4, 13.8, –4.16. m/z (GC-MS): ($C_{15}H_{29}NO_2Si$): 283 [M^+, 7%], 267 [M^+-NH_2, 32%]. M.w. (Found: 283.1957; requires: 283.1967).

2-(4-Iodopent-4-enyl)-4-methyl-6-(5-methylfuran-2-yl)-[1,3]oxazinane (13)

Iodoaldehyde **11** (0.178 g, 0.8 mmol) was added to the mixture of amino-alcohol **8** (0.138 g, 0.8 mmol) in DCM (7 mL) and 1.2 g of 3 Å molecular sieves at 0°C. The reaction mixture was stirred at room temperature for 2 h, then filtered off and the filtrate was concentrateded under reduced pressure. The residue was subjected to flash column chromatography to afford the title compound as pale yellow oil in (0.255 g) 85% yield. TLC, R_f: 0.27 (PE : DE (1 : 1)), IR ν_{max}/cm^{-1}: 3293 (br), 2955 (s), 1617 (s), 1152, 1104, 648. δ_H (300 MHz, $CDCl_3$): 6.1 (d, J 3.0 Hz, 1H), 5.9 (d, J 3.0 Hz, 1H), 5.82 (dd, J_1 1.0 Hz, J_2 2.02 Hz, 1H), 5.62 (d, J 1.5 Hz, 1H), 4.5 (dd, J_1 2.02 Hz, J_2 11.5 Hz, 1H), 4.2 (m, 1H), 3.0 (m, 1H), 2.20 (m, 2H), 2.15 (s, 3H), 1.8–1.3 (m, 6H), 1.1 (d, J 6.5 Hz, 3H). δ_C (75.5 MHz, $CDCl_3$): 153.0, 152.3, 126.0, 112.3, 108.0, 106.4, 88.4, 72.4, 50.4, 45.5, 37.9, 34.6, 25.0, 22.5, 14.0. m/z (GC-MS): ($C_{15}H_{22}INO_2$): 376 [M^+ + H,

18%], 358 [M^+-OH, 20%], 294 [M^+-C_5H_5O, 20%], 248 [M^+-I, 20%]. M.w.: (Found: 376.0711; requires: 376.0773).

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