Solvent-Free Synthesis of 2H-Pyrans: One-Pot Reactions of Dithiocarbamates, Alkyl Propiolates, and Isocyanides

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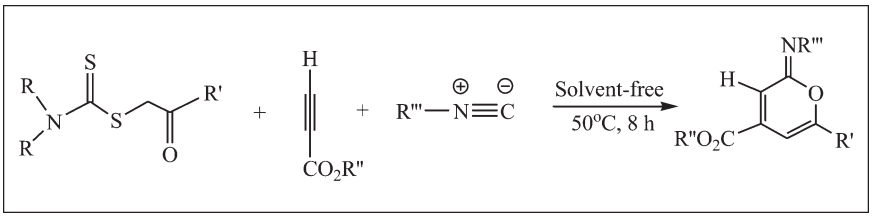

A novel, convenient, and an efficient approach to the synthesis of 2H-pyrans has been reported based on the multicomponent reaction. Solvent-free condition for the reaction of dithiocarbamates, alkyl propiolates and isocyanides lead to the formation of 2H-pyrans in good yields. In these reactions, synthesis of 2H-pyrans is possible based on the one-pot reaction and without using any catalyst. The mild reaction conditions and high yields of the products exhibit the good synthetic advantage of these methods.

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INTRODUCTION

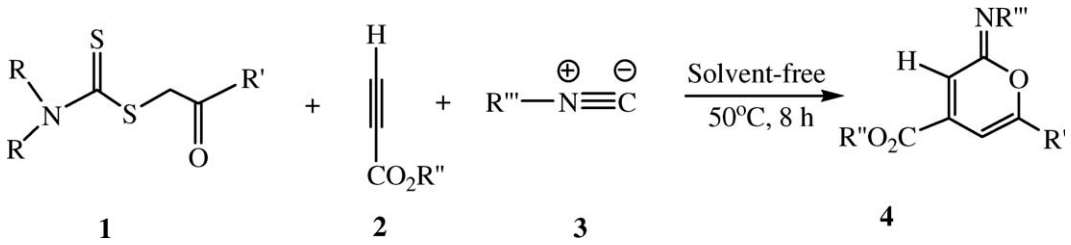
The methods of green chemistry continue to grow in importance. Alternate processes help to conserve resources and can even reduce costs. The replacement of convention solvents with water or solvent-free conditions, which is harmless to health and is available in large quantities, is one of the most interesting basic approaches along these lines. Multicomponent reactions (MCRs) have been generally used by synthetic chemists as a basic means to generate molecular diversity from bifunctional substrates that react repeatedly in an intramolecular method [1–4]. Devising such types of MCRs that inclusive the formation of multiple bonds in a single action is one of the main challenges in new organic synthesis [5–9]. They afford a great tool toward the one pot synthesis of various and complex compounds as well as small and drug-like heterocycles [10]. MCRs that involve isocyanides are by far the most flexible reactions in terms of scaffolds and number of handy compounds [1–5,11]. Here, we describe an efficient synthesis of 2H-pyran derivatives via the reaction of a dithiocarbamates, alkyl propiolates and isocyanides under solvent-free conditions at 50°C (Scheme 1).

RESULT AND DISCUSSION

As indicated in Scheme 1, dithiocarbamates 1, alkyl propiolates 2, and isocyanides 3 undergo a smooth 1:1:1 addition reaction under solvent-free conditions at 50°C to produce 2H-pyran derivatives 4 in 87–92% yields (Scheme 1). Structures of compounds 4a–4f were deduced from their IR, 1H NMR, and 13C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The 1H NMR spectrum of 4a exhibited a triplet at $\delta = 1.31$ ($3J = 7.5$ Hz) for the methyl group and four singlets for the *tert*-butyl (δ 1.25 ppm), methoxy (δ 3.78 ppm), and olefinic (δ 6.57 and 6.64 ppm) protons. The proton decoupled 13C NMR spectrum of 4a showed 12 distinct resonances in agreement with the proposed structure. Two single resonances at $\delta = 161.2$ and 162.3 ppm are observed in the 13C NMR spectrum of 4a, which are attributed to the carbonyl groups. Although we have not established the mechanism of the reactions in an experimental manner, a possible explanation is proposed in Scheme 2. Dithiocarbamates 1 were produced from the reaction of secondary amines, carbon disulfide, and alkyl bromides under solvent-free conditions. On the basis of the well-established chemistry of isocyanides [12–17], it is reasonable to assume that the compound 5 apparently results from initial addition of the isocyanide to the alkyl propiolates that adds to dithiocarbamate 1 resulting in the formation of 6, which undergoes cyclization to generate the 2H-pyrans 4a–f.

In conclusion, we have developed the most useful and dependable procedure currently available for the synthesis of 2H-pyrans by using low cost and readily available

Scheme 1



1 2 3 4

starting materials in one-pot. This method represents a simple and green procedure, uses mild reaction conditions, and has general applicability. It avoids hazardous organic solvents and toxic catalysts and gives nearly quantitative yields without any byproducts in most cases.

EXPERIMENTAL

All chemicals were obtained from commercial sources. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. 1H NMR and 13C NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform-d1, and tetramethylsilane was used as an internal standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicollet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

Typical procedure for the preparation of 2H-pyran derivatives 4. A mixture of dithiocarbamates (2 mmol) and alkyl propiolates (2 mmol) was warmed at about 50°C for 2 h. Then, the isocyanide (2 mmol) was added slowly. The reaction mixture was stirred for 8 h at room temperature, and then poured into water (15 mL). The resulting precipitate was separated by filtration and was purified from diethyl ether (Et2O) to afford the pure title compounds.

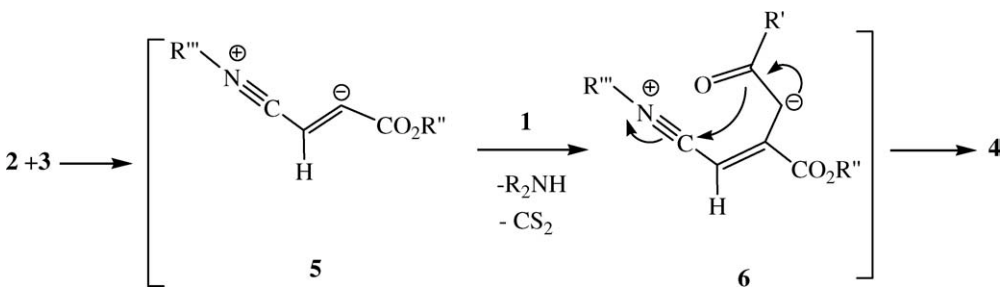
6-Ethyl 4-methyl-2-(*tert*-butylimino)-2H-pyran-4,6-dicarboxylate (4a). Pale yellow powder, mp 118–120°C, yield: 0.52 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1730, 1728, 1587, 1524 and 1224 cm^{-1}. 1H NMR: δ = 1.25 (9 H, s, Me3C), 1.31 (3 H, t, 3J = 7.5 Hz, Me), 3.78 (3 H, s, MeO), 4.34 (2 H, q, 3J = 7.5 Hz, CH2O), 6.57 (1 H, s, CH), 6.64 (1 H, s, CH) ppm. 13C NMR: δ = 14.1 (Me), 29.5 (Me3C), 52.4 (MeO), 55.5 (C—N), 63.2 (CH2O), 118.4 (CH), 119.5 (CH), 135.2 (C), 143.7 (C), 148.6 (C=N), 161.2 (C=O), 162.3 (C=O) ppm.

Methyl 2-(*tert*-butylimino)-6-(4-methylpheny)l-2H-pyran-4-carboxylate (4b). Yellow powder, mp 138–140°C, yield: 0.54 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1732, 1687, 1567, 1525 and 1248 cm^{-1}. 1H NMR: δ = 1.27 (9 H, s, CMe3), 2.36 (3 H, s, Me), 3.76 (3 H, s, MeO), 6.67 (1 H, s, CH), 6.92 (1 H, s, CH), 7.45 (2 H, d, 3J = 7.5 Hz, 2 CH), 7.82 (2 H, d, 3J = 7.5 Hz, 2 CH) ppm. 13C NMR: δ = 21.6 (Me), 31.0 (CMe3), 51.7 (MeO), 57.4 (C—N), 108.6 (CH), 112.4 (CH), 125.5 (2 CH), 129.6 (2 CH), 133.4 (C), 134.2 (C), 137.3 (C), 155.5 (C=N), 156.3 (C), 164.2 (C=O) ppm.

Eethyl 2-(*tert*-butylimino)-6-(4-nitropheny)l-2H-pyran-4-carboxylate (4c). Pale yellow powder, mp 138–140°C, yield: 0.60g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1730, 1687, 1645, 1545 and 1257 cm^{-1}. 1H NMR: δ = 1.29 (9 H, s, CMe3), 1.30 (3 H, t, 3J = 7.3 Hz, Me), 4.10 (2 H, q, 3J = 7.3 Hz, CH2O), 6.58 (1 H, s, CH), 6.86 (1 H, s, CH), 8.12 (2 H, d, 3J = 8.2 Hz, 2 CH), 8.35 (2 H, d, 3J = 8.2 Hz, 2 CH) ppm. 13C NMR: δ = 14.2 (Me), 30.5 (CMe3), 58.2 (C—N), 61.4 (CH2O), 108.7 (CH), 121.4 (CH), 126.5 (2 CH), 130.7 (2 CH), 138.5 (C), 141.6 (C), 147.6 (C), 158.4 (C), 159.2 (C=N), 162.4 (C=O) ppm. Anal. Calc. for C18H20N2O7 (344.36): C, 62.78; H, 5.85; N, 8.13 found: C, 62.65; H, 5.76; N, 8.04%.

Ethyl 2-(cyclohexylimino)-6-(4-nitropheny)l-2H-pyran-4-carboxylate (4d). Yellow powder, mp 142–144°C, yield: 0.85 g (894%). IR (KBr) (ν_{max}/cm^{-1}): 1728, 1695, 1663, 1554 and 1232 cm^{-1}. 1H NMR: δ = 1.28 (3 H, t, 3J = 7.4 Hz, Me), 1.32 (2 H, m, CH2), 1.38 (2 H, m, CH2), 1.45 (2 H, m, CH2), 1.65 (2 H, m, CH2), 1.83 (2 H, m, CH2), 3.76 (1 H, m, N-CH), 4.24 (2 H, q, 3J = 7.4 Hz, CH2O), 6.52 (1 H, s, CH), 6.74 (1 H, s, CH), 7.72 (2 H, d, 3J = 7.6 Hz, 2 CH), 7.87 (2 H, d, 3J = 7.6 Hz, 2 CH) ppm. 13C NMR: δ = 14.2 (Me), 24.5 (CH2), 24.7 (CH2), 25.8 (CH2), 34.3 (CH2), 35.0 (CH2), 57.0 (C—N), 61.8 (CH2O), 108.3 (CH), 118.4 (CH), 126.2 (2 CH), 130.7 (2 CH), 136.2 (C), 142.5 (C), 148.6 (C), 154.0 (C=N), 159.7 (C), 162.8 (C=O) ppm. Anal. Calc. for

Scheme 2



5 6

C20H22N2O5 (370.39): C, 64.85; H, 5.99; N, 7.56 found: C, 64.76; H, 5.84; N, 7.46%.

6-Ethyl 4-methyl-2-(1,1,3,3-tetramethylbutylimino)-2H-pyran-4,6-tricarboxylate (4e). Pale yellow powder, mp 132–134°C, yield: 0.62 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1725, 1720, 1685, 1584, 1423 and 1257 cm^{-1}. 1H NMR: δ = 1.12 (9 H, s, CMe3), 1.24 (3 H, t, 3J = 7.5 Hz, Me), 1.52 (3 H, s, Me), 1.55 (3 H, s, Me), 1.84 (2 H, s, CH2), 3.78 (3 H, s, MeO), 4.20 (2 H, q, 3J = 7.5 Hz, Me), 6.84 (1 H, s, CH), 6.92 (1 H, s, CH) ppm. 13C NMR: δ = 14.0 (Me), 29.5 (C), 30.2 (Me), 31.8 (CMe3), 32.3 (Me), 51.5 (MeO), 55.6 (CH2), 59.2 (C—N), 61.5 (CH2O), 109.4 (CH), 116.8 (CH), 133.5 (C), 144.5 (C), 158.6 (C), 161.5 (C=O), 163.5 (C=O) ppm. Anal. Calc. for C18H27NO5 (337.41): C, 64.08; H, 8.07; N, 4.15 found: C, 63.94; H, 7.96; N, 4.02%.

Methyl2-(2-ethoxy-2-oxoethylimino)-6-(4-methylphenyl)-2H-pyran-4-carboxylate (4f). White powder, mp 136–138°C, yield: 0.70 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1736, 1728, 1689, 1635, 1562, 1434 and 1298 cm^{-1}. 1H NMR: δ = 1.32 (3 H, t, 3J = 7.3 Hz, Me), 2.34 (3 H, s, Me), 3.78 (3 H, s, MeO), 4.25 (2 H, s, CH2), 4.26 (2 H, q, 3J = 7.3 Hz, OCH2), 6.52 (1 H, s, CH), 6.89 (1 H, s, CH), 7.53 (2 H, d, 3J = 7.8 Hz, 2 CH), 7.83 (2 H, d, 3J = 7.8 Hz, 2 CH) ppm. 13C NMR: δ = 14.0 (Me), 21.5 (Me), 51.4 (CH2-N), 52.4 (MeO), 62.3 (OCH2), 108.5 (CH), 118.6 (CH), 127.2 (2 CH), 130.4 (2 CH), 134.7 (C), 136.2 (C), 137.5 (C), 158.2 (C), 159.3 (C=N), 161.5 (C=O), 162.3 (C=O) ppm. Anal. Calc. for C18H19NO5 (329.35): C, 65.64; H, 5.81; N, 4.25 found: C, 65.52; H, 5.75; N, 4.15%.

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