ONE-POT, MILD AND EFFICIENT MULTICOMPONENT SYNTHESIS OF NOVEL VARIOUS SPIRO-NITROGEN HETEROCYCLE COMPOUNDS

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ABSTRACT. One-pot, mild and efficient synthesis of various spiro-nitrogen heterocycle compounds, based on the reaction of ninhydrin and 1,2-diaminobenzene, \((\text{indenoquinoxalin})\), with \(N\)-heterocycle compounds and dialkylacetylenedicarboxylates is described. Using this approach, various spiro-nitrogen heterocycle compounds at a temperature of 50-60 °C in acetonitrile solvent, can be obtained very high yields.

KEY WORDS: Ninhydrin, 1,2-Diaminobenzene, spiro-Nitrogen heterocycle compounds, Indenoquinoxalin, N-heterocycle compounds, Dialkylacetylenedicarboxylates

INTRODUCTION

Heterocyclic chemistry is one of the most complex branches of chemistry and heterocyclic compounds, the largest and most diverse family of chemical compounds. The heterocyclic compounds have a stable structure that cannot be easily hydrolyzed or polymerized [1-3]. The heterocyclic compounds are a broad category of ring compounds that contain one or more non-carbon atoms, including nitrogen, oxygen, sulfur, or phosphorus in their structure [4-6].

Heterocyclic compounds play a vital role in biological processes and are widely found in natural compounds [7-11]. The main source of these compounds is plants. Heterocyclic compounds are used in the pharmaceutical industry. Some vitamins, proteins, and hormones have a heterocyclic structure. Multi-component reactions have always been a beneficial way of synthesizing heterocyclic compounds [12-17]. The quinoline, isoquinoline and \(\text{indenoquinoxalin}\) skeleton compounds are often used for the design of many synthetic compounds with diverse pharmacological properties such as antimicrobial, cytotoxic, HIV protease inhibitor, anti-inflammatory, anti-cancer, antitumor, antimalarial and anti-viral activities [18-20]. Yavari and co-workers had reported a huge number studies, utilizing quinoline, isoquinoline, \(\text{indenoquinoxalin}\) and acetylendicarboxylate esters [21-27].

Meanwhile, \(\text{indenoquinoxalin}\) is one of the most important compounds for the synthesis of many heterocyclic compounds using multiple reactions [28-34]. The extent and dynamics of this part of organic chemistry has made these compounds a special place. Hence, researchers are using new and modern techniques to produce heterocyclic compounds [35-44].

According to the introduction, in this paper, using a gentle, effective and one-pot method, we reported an effective synthesis of spiro-heterocyclic nitrogen compounds based on the reaction between ninhydrin and 1,2-diaminobenzen, \((\text{indenoquinoxalin})\), with heterocyclic nitrogen compounds and dialkylacetylenedicarboxylate. Based on this, various spiro-nitrogen heterocycle compounds at a temperature of 50-60 °C in acetonitrile solvent, can be obtained very good yields.

RESULTS AND DISCUSSION

Initially, for the sample the reaction of ninhydrin 1 with 1,2-diaminobenzene 2 with isoquinoline 3 and dimethylacetylenedicarboxylate 4 was selected. In this case, solvent optimization and
reaction conditions were performed. Acetonitrile was found to be a suitable solvent and the best yield of 5a was obtained at a temperature of 50-60 °C in acetonitrile. In the following, the reaction of ninhydrin 1 and 1,2-diaminobenzene 2 with nitrogen heterocycle compounds 3 and dialkylacetylenedicarboxylate 4 in an acetonitrile solvent is complete at 50-60 °C for 12 hours and spiro-heterocyclic nitrogen-containing compounds 5a-f produce very good yields (Scheme 1-3).

According to the results, products have two diastereomeric forms (60:40). But it is noteworthy that the reaction between dimethylacetylenedicarboxylate with pyridine or isoquinoline or quinoline and N-heterocycle compounds generates only one diastereoisomer, while with diethylacetylenedicarboxylate produce two diastereo isomers. Unfortunately, we could not separate these diastereoisomers (Scheme 4).

Scheme 1. Formation of spiro-nitrogen heterocycle compounds 5a–5b.

Scheme 2. Formation of spiro-nitrogen heterocycle compounds 5c–5d.

Scheme 3. Formation of spiro-nitrogen heterocycle compounds 5e–5f.

The structure of the spiro-heterocyclic nitrogen compounds 5a-f is deduced from the $^1$H NMR, $^{13}$C NMR and IR spectra and elemental analysis. For example, the spectrum of the $^1$H NMR composition of 5a in CDCl$_3$ showed a singlet at $\delta$ 3.23 and a singlet at $\delta$ 4.07 for the methoxyprotons (2OMe), a doublet at $\delta$ 5.91 and a doublet at $\delta$ 6.57 for the methine proton ($=CH_{dihydroisoquinoline}$), a singlet at $\delta$ 6.88 for the (CH$_{diastereoisomer}$) proton, multiplets at $\delta$ 7.40 for aryl protons (12H). The spectrum of the $^{13}$C NMR composition of 5a in CDCl$_3$ showed 30 distinct resonances in agreement with the proposed structure.
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Scheme 4. Two diastereoisomers of spiro-nitrogen heterocycle compounds 5b, 5d and 5f.

The proposed mechanism for the synthesis of various spiro-nitrogen heterocycle compounds can be shown below (Scheme 5). Initially, in the reaction vessel, ninhydrin 1 reacted with 1,2-diaminobenzene 2 and produced an intermediate of the indenoquinoxalin 6. At the same time, nitrogen isoquinoline 3 attacked the dialkylacetylenedicarboxylate 4 and produced an intermediate 7. Then, the carbonyl group of intermediate 6 was attacked by carbon with a negative average of intermediate 7 to furnish intermediate 8. In the following, by forming a ring, the final product 5 is produced.

Scheme 5. A plausible mechanism for compound 5.

EXPERIMENTAL

Chemicals and apparatus

Solvents, ninhydrin, 1,2-diaminobenzene, isoquinoline, quinoline, pyridine and dialkylacetylenedicarboxylate were obtained from Merck, Fluka, and Aldrich, and were used without further purification. Electrothermal-9100 was used to measure the melting temperature. Elemental analysis was performed with Heraeus CHN-O-Rapid. 1H, 13C NMR spectra were recorded with a Bruker DRX-500 Avance instrument using CDCl3 as the deuterated solvent containing TMS as internal standard, at 300, 500.1, 125.8 MHz, respectively; δ in ppm, J in Hz. IR Spectra (ν/cm⁻¹) were recorded as KBr pellets with a Shimadzu IR-460 spectrometer.

To a mixture of (1 mmol) ninyhydrin and (1 mmol) of 1,2-diaminobenzene in 10 mL of acetonitrile solvent, (1 mmol) isoquinoline was added and the solution was stirred. Then (1 mmol) of diallylacetiledicarboxylate in 2 mL of acetonitrile was dropwise added to the solution for 15 min at room temperature. Then the reaction mixture was allowed to warm to 50-60 °C and was stirred for 12 hours. The product was filtered and the solvent was removed under reduced pressure. The remaining residue was recrystallized and poured from ethanol.

**Diethyl 11b'H-spiro[indeno[1,2-b]quinoxaline-11,2'-[1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5a).** Yellow powder; m.p. = 240; yield: 0.462 g (87%); IR (KBr) (νmax/cm⁻¹) = 1707, 1736 (2C=O); 1H NMR: δ 3.32 (3H, s, MeO), 4.07 (3H, s, MeO), 5.91 (1H, d, J = 7.9 Hz, =CH), 6.57 (1H, d, J = 7.9 Hz, =CH), 6.88 (1H, s, CH), 7.8-4.0 (12H, m, =CH); 13C NMR: δ 13.19 (Me), 13.96 (Me), 60.19 (OCH₃), 80.77 (CH), 104.79 (Cₚ), 122.33, 123.44, 124.09, 125.12, 126.45, 126.98, 127.82, 129.09, 129.40, 129.84, 129.91, 130.28, 130.41 (14=CH), 131.81, 131.24, 137.12, 138.26, 141.32, 142.53, 145.75, 147.65, 149.01, 154.23 (10C), 163.19, 163.39 (2C=O); NMR data for the minor isomer (40%): 1H NMR: δ 0.57 (3H, t, J = 7.1 Hz, Me), 1.49 (3H, t, J = 7.1 Hz, Me), 3.60 (2H, m, OCH₃), 4.53 (2H, m, OCH₂), 5.89 (1H, d, J = 7.8 Hz, =CH), 6.59 (1H, d, J = 7.7 Hz, =CH), 6.90 (1H, s, CH), 7-8.30 (12H, m, =CH); 13C NMR: δ 13.19 (Me), 13.96 (Me), 60.19 (OCH₃), 80.77 (OCH), 104.79 (Cₚ), 122.33, 123.44, 124.09, 125.12, 126.45, 126.98, 127.82, 129.09, 129.40, 129.84, 129.91, 130.28, 130.41 (14=CH), 131.81, 131.24, 137.12, 138.26, 141.32, 142.53, 145.75, 147.65, 149.01, 154.23 (10C), 163.19, 163.39 (2C=O); IR (KBr) (νmax/cm⁻¹) = 1703, 1735 (2C=O); NMR (503.15): C, 71.56; H, 4.20; N, 8.35; O, 15.89%. Found: C, 71.54; H, 4.23; N, 8.32; O, 15.91%.

**Diethyl 11b'H-spiro[indeno[1,2-b]quinoline-11,2'-[1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate (5b).** Yellow powder; m.p. = 240; yield: 0.462 g (87%); IR (KBr) (νmax/cm⁻¹) = 1707, 1736 (2C=O); νmax/cm⁻¹ = 1703, 1735 (2C=O); IR (KBr) (νmax/cm⁻¹) = 1707, 1713 (2C=O); 1H NMR: δ 3.32 (3H, s, MeO), 3.93 (3H, s, MeO), 5.95 (1H, dd, J = 9.8 Hz, =CH), 6.52 (1H, d, J = 4.3 Hz, =CH), 6.83 (1H, d, J = 9.8 Hz, =CH), 7.05-8.12 (12H, m, =CH); 13C NMR: δ 13.11 (Me), 13.93 (Me), 60.24 (OCH₃), 80.79 (CH), 106.13 (Cₚ), 122.68, 123.91, 125.07, 125.21, 126.24, 126.96, 127.36, 128.79, 128.85, 129.46, 129.79, 129.86, 130.05, 130.12 (14=CH), 131.81, 131.14, 137.12, 138.26, 141.32, 142.88, 145.75, 147.65, 149.01, 154.23 (10C), 162.21, 162.42 (2C=O). Anal. calcld. for C₂₈H₂₆N₂O₅: C, 72.31; H, 4.74; N, 7.91; O, 15.05%. Found: C, 72.28; H, 4.70; N, 7.93; O, 15.10%.

**Diethyl 4a'H-spiro[indeno[1,2-b]quinoline-11,3'-[1,3]oxazino[3,2-a]quinoline]-1',2'-dicarboxylate (5c).** Yellow powder; m.p. = 240; yield: 0.409 g (77%); IR (KBr) (νmax/cm⁻¹) = 1726 (2C=O); νmax/cm⁻¹ = 1707, 1713 (2C=O); NMR data for the major isomer (60%): 1H NMR: δ 0.60 (3H, t, J = 7.1 Hz, Me), 1.31 (3H, t, J = 7.1 Hz, Me), 3.72 (2H, m, OCH₂), 4.41 (2H, m, OCH₂), 5.95 (1H, dd, J = 9.6 Hz, =CH), 6.01 (1H, d, J = 4.7 Hz, =CH), 6.88 (1H, d, J = 9.6 Hz, =CH), 7.02-8.20 (12H, m, =CH); 13C NMR: δ 13.18 (Me), 13.96 (Me), 60.20 (OCH₂), 62.78 (OCH₂), 81.03 (CH), 114.31 (Cₚ).
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118.58, 121.79, 122.42, 122.45, 123.75, 128.65, 128.93, 129.22, 129.24, 129.27, 129.79, 129.84, 129.93 (14=CH), 130.42, 131.18, 135.89, 138.29, 141.41, 142.89, 143.67, 146.46, 154.01, 161.24 (10C), 164.02, 164.45 (2C=O); NMR data for the minor isomer (40%): 1H NMR: δ 0.59 (3H, t, J = 7.1 Hz, Me), 1.31 (3H, t, J = 7.1 Hz, Me), 3.60 (2H, m, OCH_2), 4.32 (2H, m, OCH_2), 5.95 (1H, dd, J = 9.6 Hz, =CH), 6.01 (1H, d, J = 4.7 Hz, =CH), 6.88 (1H, d, J = 9.6 Hz, CH), 7.02-8.20 (12H, m, =CH); 13C NMR: δ 13.18 (Me), 13.96 (Me), 60.20 (OCH_2), 62.78 (OCH_2), 79.93 (CH), 114.31 (C_{spiro}), 118.58, 121.79, 122.42, 122.45, 123.75, 128.65, 128.93, 129.22, 129.24, 129.27, 129.79, 129.84, 129.93 (14=CH), 130.42, 131.18, 135.89, 138.29, 141.41, 142.89, 143.67, 146.46, 154.01, 161.24 (10C), 164.02, 164.45 (2C=O). Anal. calcd. for C_{23}H_{23}N_5O_5 (531.18): C, 72.31; H, 4.74; N, 7.91; O, 15.05%. Found: C, 72.35; H, 4.73; N, 7.89; O, 15.07%.

**Dimethyl 9a’H-spiro[indeno[1,2-b]quinoline-11,2’-pyrido[2,1-b] [1,3]oxazine]-3’,4’-dicarboxylate (5e)**. Yellow powder; m.p. = 192 °C; yield: 0.390 g (86%); IR (KBr) (ν\text{max} cm\(^{-1}\)) = 1737 (2C=O), 1259; 1H NMR: δ 1.15 (6H, s, 2MeO), 5.32 (1H, dd, J = 6.7 Hz, =CH), 5.49 (1H, dd, J = 9.9 Hz, =CH), 6.20 (1H, dd, J = 9.9 Hz, =CH), 6.45 (1H, d, J = 7.5 Hz, =CH), 6.96 (1H, dd, J = 3.2 Hz, CH), 7.42-8.17 (8H, m, =CH); 13C NMR: δ 53.42, 57.99 (2Me), 79.37 (CH), 101.69 (C_{spiro}), 107.28, 116.48, 122.42, 123.66, 124.84, 125.11, 128.93, 129.04, 129.73, 129.91, 130.34 (12=CH), 132.09, 132.85, 141.27, 142.50, 145.50, 147.28, 153.91, 161.70 (8C), 163.54, 163.77 (2C=O). Anal. calcd. for C_{23}H_{23}N_5O_5: (453.45): C, 68.87; H, 4.22; N, 9.27; O, 17.64%. Found: C, 68.79; H, 4.23; N, 9.30; O, 17.66%.

**Diethyl 9a’H-spiro[indeno[1,2-b]quinoline-11,2’-pyrido[2,1-b] [1,3]oxazine]-3’,4’-dicarboxylate (5f)**. Yellow powder; m.p. = 192 °C; yield: 0.380 g (79%); IR (KBr) (ν\text{max} cm\(^{-1}\)) = 1695, 1734 (2C=O); NMR data for the major isomer (60%): 1H NMR: δ 0.50 (3H, t, J = 7.1 Hz, Me), 1.44 (3H, t, J = 7.1 Hz, Me), 3.59 (2H, m, OCH_2), 4.48 (2H, m, OCH_2), 5.35 (1H, dd, J = 10 Hz, =CH), 5.54 (1H, dd, J = 9.9 Hz, =CH), 6.24 (1H, dd, J = 9.9 Hz, =CH), 6.51 (1H, d, J = 7.6 Hz, =CH), 7.03 (1H, dd, J = 3.2 Hz, CH), 7.50-8.16 (8H, m, =CH); 13C NMR: δ 13.15 (Me), 13.96 (Me), 60.23 (OCH_2), 62.78 (OCH_2), 79.93 (CH), 101.38 (C_{spiro}), 107.19, 116.47, 122.27, 123.81, 124.84, 125.11, 128.84, 129.16, 129.78, 130.23 (12=CH), 132.04, 138.53, 141.24, 142.69, 145.76, 147.56, 154.12, 161.91 (8C), 163.08, 163.35 (2C=O). Anal. calcd. for C_{23}H_{23}N_5O_5 (481.51): C, 69.84; H, 4.81; N, 8.73; O, 16.61%. Found: C, 69.80; H, 4.83; N, 8.75; O, 16.60%.

**CONCLUSIONS**

In this work, one-pot, mild and efficient synthesis of various spiro-nitrogen heterocycle compounds based on the reaction of ninhydrin and 1,2-diaminobenzene with isoquinoline or quinoline or pyridine and dialkylacetylenedicarboxylate in CH\(_2\)CN at 50-60 °C is described. Using this approach, all spiro-nitrogen heterocycle compounds are obtained in high yields. The method offers several advantages including high diversity via various functional groups, operational simplicity and high yields.

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