Three Component Synthesis of Substituted 4*H*-[1,3]Dioxin Derivatives Under Solvent-Free Conditions

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Abstract: Reaction between aryl aldehydes, acetylacetone and alkyl isocyanides in solvent-free conditions provided a simple and efficient one-pot route for the synthesis of 1-(2-alkylamino-6-methyl-4-aryl-4*H*-[1,3]dioxin-5-yl)ethanone derivatives in excellent yields.

Keywords: Multicomponent reactions, Acetylacetone, Aryl aldehydes, Alkyl isocyanides, Solvent-free, Substituted 4*H*-[1,3]dioxins.

Introduction

Isocyanides, as the only class of stable organic compounds with a two-valence carbon atom, are very reactive species and react with many functional groups through different mechanisms. On the basis of valence-bond theory, isocyanide functionality can be shown as two resonance forms **I** and **II** (Figure 1). So, isocyanides have carbonic character on the basis of resonance form **I** and nucleophilic character on the basis of form **II**. On the other hand, isocyanides are dual characteristic and their reactivity is toward reaching the stable bonding state of four-valence carbon. In the most addition reactions of isocyanides both the nucleophile and electrophile add to the α -carbon atom, and no species is added to the nitrogen.

Figure 1. Two resonance forms.

The addition reaction of different compounds to isocyanides has been of particular interest since many years ago. For example, the reaction of hydrogen halides to isocyanides at low temperatures has been reported to produce holoimines¹. The addition of hydrazoic acid to isocyanides was reported to produce tetrazole derivatives². The reaction of organic acids, such as Meldrom's acid³ or 1,1,1-trifluoro-2,3-pentandiones⁴, on isocyanides was also reported. Isocyanides have been reported to react with two equivalent of carboxylic acids to afford the corresponding carboxylic formamide and carboxylic anhydride⁵. Recently it has been reported that the reaction of isocyanides with sulfonic acids lead to the corresponding sulfonamides.⁶ Three-component condensation reactions of cyclic 1,3-diketones, 4-nitrobenzaldehyde and alkyl or aryl isocyanides efficiently occurs in water without a catalyst at 75°C within one hour providing a convenient synthesis of substituted tetrahydrobenzofurans⁷. On the course of works with isocyanides⁸⁻¹⁴, we report herein that the reaction between aryl aldehydes, acetylacetone and alkyl isocyanides in solvent-free conditions produces 1-(2-alkylamino-6-methyl-4-aryl-4*H*-[1,3]dioxin-5-yl)ethanone derivatives in excellent yields.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ¹H and ¹³C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in CDCl₃ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General Procedure for Preparation of Compounds 4a-e

A mixture of acetylacetone (2 mmol), aryl aldehyde (2 mmol) and alkyl isocyanides (1 mmol) was stirred in an oil bath at 100°C and the reaction was followed by TLC. After completion, diethyl ether (10 mL) was added to the reaction mixture and the product was filtered off and washed with diethyl ether (10 mL).

1-(2-Cyclohexylamino-6-methyl-4-phenyl-4*H*-[1,3]dioxin-5-yl)ethanone (4a)

White powder; m.p. 132-134°C. IR (KBr) (ν_{max} , cm⁻¹): 3305 (NH), 1669 (C=O). Analyses: Calcd. for C₁₉H₂₅NO₃: C, 72.35; H, 7.99; N, 4.44%. Found: C, 72.5; H, 7.8; N, 4.5%. MS (*m/z*, %): 315 (M⁺, 3), 43 (COCH₃, 12), 105 (COPh, 100), 77 (Ph, 25). ¹H NMR (500 MHz, CDCl₃): δ 1.12-2.28 (10 H, m, 5 CH₂ of cyclohexyl), 1.58 and 1.92 (6 H, 2s, 2 CH₃), 3.82 (1H, m, CH of cyclohexyl), 6.02 (1 H, d, ³*J*_{HH} = 7 Hz, NH), 6.31 (1H, s, CH), 7.37-7.65 (5 H, m, 5 CH aromatic), 8.95 (1H, d, ³*J*_{HH} = 7 Hz, CHN). ¹³C NMR (125.8 MHz, CDCl₃): δ 24.65 and 32.82 (2CH₃), 24.68, 25.41, 33.92 (5 CH₂ of cyclohexyl), 48.01 (CH of cyclohexyl), 75.88 (CH), 127.40 (CHN), 128.77, 128.64, 129.76, 133.63, 141.52, 165.36 (C=C and 4C aromatic), 181.70 (C=O).

1-[2-Cyclohexylamino-6-methyl-4-(4-nitrophenyl)-4*H*-[1,3]dioxin-5-yl]ethanone (4b)

White powder; m.p. 114-116°C. IR (KBr) (ν_{max} , cm⁻¹): 3256 (NH), 1660 (C=O). Analyses: Calcd. for C₁₉H₂₄N₂O₅: C, 63.32; H, 6.71; N, 7.77%. Found: C, 63.2; H, 6.8; N, 7.9%. MS (*m/z*, %): 360 (M⁺, 7), 43 (COCH₃, 55), 83 (cyclohexyl, 60), 150 (COC₆H₄NO₂, 100), 277(M - cyclohexyl, 20). ¹H NMR (500 MHz, CDCl₃): δ 1.11-2.40 (10 H, m, 5 CH₂ of cyclohexyl), 1.73 and 1.93 (6 H, 2s, 2 CH₃), 3.80 (1H, m, CH of cyclohexyl), 5.96 (1 H, d, ³*J*_{HH} = 7 Hz, NH).

6.32 (1H, s, CH), 7.64 (1H, d, $^3J_{\text{HH}} = 7$ Hz, CHN), 7.74 and 8.36 (4 H, 2d, $^3J_{\text{HH}} = 10$ Hz, 4 CH aromatic). ^{13}C NMR (125.8 MHz, CDCl_3): δ 24.66 and 32.80 (2CH₃), 24.68, 25.30, 32.90 (5 CH₂ of cyclohexyl), 48.77 (CH of cyclohexyl), 75.59 (CH), 130.99 (CHN), 124.08, 128.31, 134.00, 141.74, 149.80, 165.44 (C=C and 4C aromatic), 180.83 (C=O).

1-[2-Cyclohexylamino-6-methyl-4-(3-nitrophenyl)-4H-[1,3]dioxin-5-yl]ethanone (4c)

White powder; m.p. 121 – 123°C. IR (KBr) (ν_{max} , cm^{-1}): 3315 (NH), 1665 (C=O). MS (m/z , %): 360 (M^+ , 11). Analyses: Calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_5$: C, 63.32; H, 6.71; N, 7.77%. Found: C, 63.2; H, 6.8; N, 7.9%. MS (m/z , %): 360 (M^+ , 7), 43 (COCH_3 , 100), 83 (cyclohexyl, 20), 98 ($\text{C}_6\text{H}_{11}\text{NH}$, 80), 315 ($\text{M} - \text{NO}_2$, 35), 277 ($\text{M} - \text{cyclohexyl}$, 35). ^1H NMR (500 MHz, CDCl_3): δ 1.10–2.24 (10 H, m, 5 CH₂ of cyclohexyl), 1.69 and 1.94 (6 H, 2s, 2 CH₃), 3.83 (1H, m, CH of cyclohexyl), 6.07 (1 H, d, $^3J_{\text{HH}} = 7$ Hz, NH), 6.35 (1H, s, CH), 7.96 (1H, d, $^3J_{\text{HH}} = 7$ Hz, CHN), 7.36–8.90 (5 H, m, 5 CH aromatic). ^{13}C NMR (125.8 MHz, CDCl_3): δ 24.62 and 32.78 (2CH₃), 24.66, 25.31, 32.87 (5 CH₂ of cyclohexyl), 48.75 (CH of cyclohexyl), 75.53 (CH), 128.36 (CHN), 122.37, 124.74, 130.19, 133.82, 135.45, 137.05, 148.40, 165.60 (C=C and 6C aromatic), 180.94 (C=O).

1-[2-Tert-butylamino-6-methyl-4-(4-nitrophenyl)-4H-[1,3]dioxin-5-yl]ethanone (4d)

White powder; m.p. 96–98°C. IR (KBr) (ν_{max} , cm^{-1}): 3312 (NH), 1674 (C=O). Analyses: Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5$: C, 61.07; H, 6.63; N, 8.38%. Found: C, 61.2; H, 6.7; N, 8.4%. MS (m/z , %): 334 (M^+ , 5), 43 (COCH_3 , 100), 57 (t-Bu, 30), 150 ($\text{COC}_6\text{H}_4\text{NO}_2$, 75). ^1H NMR (500 MHz, CDCl_3): δ 1.42 (9 H, s, 3 CH₃), 1.70 and 1.91 (6 H, 2s, 2 CH₃), 5.99 (1 H, d, $^3J_{\text{HH}} = 7$ Hz, NH), 6.37 (1H, s, CH), 7.60 (1H, d, $^3J_{\text{HH}} = 7$ Hz, CHN), 7.78 and 8.39 (4 H, 2d, $^3J_{\text{HH}} = 10$ Hz, 4 CH aromatic). ^{13}C NMR (125.8 MHz, CDCl_3): δ 24.66 and 32.80 (2CH₃), 29.03 (3 CH₃), 51.67 (C), 75.51 (CH), 128.94 (CHN), 124.12, 127.98, 133.87, 140.85, 149.73, 165.22 (C=C and 4C aromatic), 180.52 (C=O).

1-[2-Tert-butylamino-6-methyl-4-(3-nitrophenyl)-4H-[1,3]dioxin-5-yl]ethanone (4e)

White powder; m.p. 88–90°C. IR (KBr) (ν_{max} , cm^{-1}): 3304 (NH), 1670 (C=O). Analyses: Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5$: C, 61.07; H, 6.63; N, 8.38%. Found: C, 61.2; H, 6.7; N, 8.4%. MS (m/z , %): 334 (M^+ , 8), 43 (COCH_3 , 80), 57 (t-Bu, 50), 109 ($\text{C}_6\text{H}_4\text{NO}_2$, 100), 150 ($\text{COC}_6\text{H}_4\text{NO}_2$, 20). ^1H NMR (500 MHz, CDCl_3): δ 1.42 (9 H, s, 3 CH₃), 1.70 and 1.91 (6 H, 2s, 2 CH₃), 5.99 (1 H, d, $^3J_{\text{HH}} = 7$ Hz, NH), 6.37 (1H, s, CH), 7.60 (1H, d, $^3J_{\text{HH}} = 7$ Hz, CHN), 7.78 and 8.39 (4 H, 2d, $^3J_{\text{HH}} = 10$ Hz, 4 CH aromatic). ^{13}C NMR (125.8 MHz, CDCl_3): δ 24.51 and 32.84 (2CH₃), 29.08 (3 CH₃), 51.62 (C), 75.39 (CH), 128.70 (CHN), 122.45, 124.80, 130.04, 133.85, 135.28, 136.94, 148.38, 165.55 (C=C and 6C aromatic), 180.72 (C=O).

Results and Discussion

The reaction of acetylacetone **1** with aryl aldehydes **2** in the presence of alkyl isocyanides **3** in solvent-free conditions at 100°C, leads to 1-(2-alkylamino-6-methyl-4-aryl-4H-[1,3]dioxin-5-yl)ethanones **4** in high yields (Figure 2).

To study the scope of the reaction, a series of aldehydes were applied. When aliphatic aldehydes or aromatic aldehydes substituted with electron-donating groups were employed, no cyclization product was detected. In all cases, aromatic aldehydes substituted with electron-withdrawing groups gave the products in good yields. The reaction was completed after 12 h (the reaction progress was monitored by TLC) **4b** was obtained in 92% yield (Figure 2 entry 2).

Similar reaction was also reported between cyclohexyl isocyanide, aliphatic, or aryl aldehydes, and 1,3-dicarbonyl compounds catalyzed by piperidine to afford 5-hydroxy-

2-hpyrrol-2-one¹⁵. The reaction mechanism for the formation of 5-hydroxy-2-hpyrrol-2-one is considered analogous to the reported mechanism of Quai¹⁶.

Figure 2. Three-component reaction of alkyl isocyanides, aryl aldehydes, and acetylacetone in solvent-free conditions.

The structures of compounds **4a-e** were deduced from their elemental analyses and IR, ¹H NMR, ¹³C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. The ¹H NMR spectrum of **4b** exhibited two single sharp lines readily recognized as arising from methyl ($\delta = 1.73$ and 1.93 ppm), and methine ($\delta = 6.32$ ppm) proton, and the aromatic protons resonate as two doublets ($^3J_{\text{HH}} = 10$ Hz) at 7.74 and 8.36 ppm. The CH proton was appeared as a multiplet at 3.80 ppm and the signals related to methylene groups of cyclohexyl moiety were observed as multiplets at 1.11 - 2.40 ppm. Doublet ($^3J_{\text{HH}} = 7$ Hz) at 7.64 was observed for proton NCH and NH proton resonated as doublet ($^3J_{\text{HH}} = 8$ Hz) at 5.96 ppm that disappeared after addition of a few drops of D₂O to CDCl₃ solution of compound **4b**. The ¹³C NMR spectrum of **4b** showed fifteen distinct resonances in agreement

with the proposed structure. The IR spectrum of compound **4b** showed strong absorption bands at 3256 and 1660 cm^{-1} for NH and carbonyl group, respectively.

The proposed mechanism for the formation of compounds **4** includes several stages; at the first intermediate **5** is formed from the proton transfer between acetylacetone and alkyl isocyanide. Then, intermediate **5** and aldehyde is converted to product **6** which could undergo stepwise cyclization to produce **4** (Figure 3).

Figure 3. Suggested mechanism for formation of compound **4**.

Conclusion

In conclusion, we have developed a highly efficient synthesis of substituted 4*H*-[1,3]dioxin derivatives from aryl aldehydes, acetylacetone and alkyl isocyanides in solvent-free conditions. The advantages of the reported method are inexpensive and easily available starting materials, simple reaction conditions, high yields, single-product reaction, and simple workup procedure.

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