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Synthesis of Ethyl 3,5-(Disubstituted Phenyl)-2-Isocyano-5-Oxopentanoate

Kawsari Akhter[1*], Roksana Akhter[1], S. Mosaddeq Ahmed[2], and Md. Ershad Halim[1]

[1]*Department of Chemistry, University of Dhaka, Dhaka 1000, Bangladesh*
[2]*Department of Natural Science (Chemistry), American International University – Bangladesh (AIUB) 408/1 Kuratoli, Khilkhet, Dhaka-1229, Bangladesh*

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Abstract

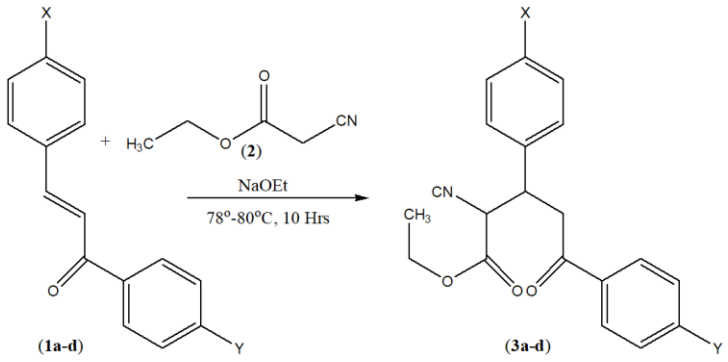
The reactions between substituted chalcones 1a-d with ethyl cyanoacetate 2 were carried out in 1:1 molar ratio in the presence of sodium ethoxide as catalyst under refluxing condition to synthesize few chalcone derivatives, ethyl 3,5-(disubstituted phenyl)-2-isocyano-5-oxopentanoate, 3a-d. The structure of the compounds was determined by their chemical properties, UV, FT-IR, 1H-NMR, 13C-NMR, mass spectral data and elemental analyses.

Keywords: Chalcones, ethyl cyanoacetate, sodium ethoxide, Michael addition

I. Introduction

Chalcones are a large family of natural compounds that are commonly found in fruits, vegetables, spices, tea, and meals based on soy. Because of their intriguing pharmacological properties, chalcones have recently been the focus of extensive research[1-3]. Chemically, they are made up of open-chain flavonoids with a three-carbon *α, β*-unsaturated carbonyl system connecting the two aromatic rings. It is a distinct template molecule connected to multiple biological processes. Interest in using chalcones or chalcone-rich plant extracts as medications or food preservatives has increased due to the phenolic groups' capacity to quench radicals[4]. Benzaldehyde and acetophenone typically undergo an aldol condensation to produce chalcones, which are significant and potentially physiologically active substances[5]. Numerous beneficial qualities of chalcones have been reported, such as their anti-inflammatory[6-7], antifungal[8-10], antioxidant[11], cytotoxic[12], and anticancer[13–16] actions.

On the other hand, because of its range of functional groups and chemical reactivity, ethyl cyanoacetate is a valuable starting material for synthesis[17]. The versatile synthetic building block ethyl cyanoacetate has three distinct reactive centers: nitrile, ester, and acidic methylene site. This allows it to use to create a wide range of functional and pharmacologically active compounds. Moreover, it can be utilized to create nitriles, acids, amides, and esters[18]. It can be employed in condensation reactions such as the Michael addition[19-20] or the Knoevenagel condensation[21-22] because it has an acidic methylene group that is bordered by both nitrile and carbonyl. This reactivity is comparable to malonic acid esters. Diethyl malonate is produced from cyanoacetic acid ethyl ester by reacting with ethanol in the presence of strong acids, serving as an illustration of reactivity with nitrile[23]. This produces the dimeric 3-amino-2-cyano-2-pentendiaciddiethyl ester when heated in the presence of sodium ethoxide[24].



Products	X	Y
3a	4-$OCH_3$4-Br	
3b	4-$OCH_3$4-Cl	
3c	4-CH_3	4-Cl
3d	4-Cl	4-Cl

Scheme 1. Synthesis of compounds, **3a-d** using sodium ethoxide as a catalyst.

In addition to their biological significance, several chalcone derivatives have been shown to be antimitotic agents due to their ability to prevent tubulin from polymerizing into microtubules[25-28]. Chalcone derivatives are also effective in slowing the progression of multiple sclerosis because they prevent the disease's myelin sheath from being destroyed in the central nervous system of affected individuals[29]. Numerous studies have observed at the Michael addition reactions of chalcones with active methylene compounds like 1,3-dicarbonyls[30–33] and ethyl acetoacetate[34].

The synthesis of a few chalcone derivatives (**3a**–**d**) in the presence of sodium ethoxide is presented in this study. The

*Author for correspondence. e-mail: kawsariakhter@du.ac.bd

produced molecules are thought to be helpful intermediates in synthetic organic chemistry and may have a range of chemical uses.

II. Materials and Methods

The mp, UV, IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elemental analyses were used to characterize each product. All the chemicals were bought from E. Merck. On plates that had been percolated with silica gel 60 F_{254}, thin layer chromatography (TLC) was done, and spots were found using iodine vapor. Uncorrected melting points were determined using an Electro Thermal Micro Melting Point equipment. The IR spectra of the samples were recorded between 4000 and 400 cm^{-1} on a Shimadzu IR 470A spectrophotometer. The ultraviolet spectra of the samples were captured using a Shimadzu UV-160A spectrometer with an 800-200 nm scanning range. Chloroform solution was used to record the spectra for solid materials. The ^{1}H-NMR and ^{13}C-NMR spectra of the samples were measured using DMSO-d_6 as the solvent and tetramethylsilane (TMS) as an internal standard on a Bruker 400 MHz spectrophotometer.

General Procedure

A mixture of substituted chalcones (0.005M) and ethyl cyanoacetate (0.005M) were taken in sodium ethoxide (25 mL) in a round bottomed flask to carry out reaction under refluxing condition (78^0-80^0C) on a magnetic stirrer for 10 hours. The progress of the reactions was followed by TLC and the mixture was cooled and neutralized with 0.1N HCl. The solid product was filtered off and recrystallized from absolute alcohol. The pure product was filtered off and washed with ice cold absolute alcohol. Then it was dried first in the air and then in a vacuum desiccator.

Ethyl 5-(4-bromophenyl)-2-isocyano-3-(4-methoxyphenyl)-5-oxopentanoate, 4a: Yield 26%; white crystalline solid; mp 114-116°C; R_f value in TLC: 0.67 (chloroform: pet-ether, 3:2); UV (λ_{max} in nm): 257 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O), 223 ($\pi\rightarrow\pi^*$ of C=C-C=O); IR (KBr) (υ_{max} in cm^{-1}): 3010, 2931 (C-H stretching), 2244 (-CN stretching), 1745, 1679 (-C=O stretching), 1585, 1515 (C=C stretching of arom.), 1399 (-CH_3 bending), 1183, 1032 (C-O-C stretching), 882, 827, 797 (=C-H of aromatic ring), 590 (C-Br stretching); ^{1}H-NMR (δ in ppm): 7.78 (d, J=7.6 Hz, 2H, C-2',6'), 7.58 (d, J=7.6 Hz, 2H, C-3',5'), 7.26 (d, J=7.2 Hz, 2H, C-2",6"), 6.84 (d, J=7.6 Hz, 2H, C-3",5"), 4.26 (q, J=7.2 Hz, 2H, -OC<u>H</u>$_2$CH$_3$), 4.09-4.03 (m, 1H, C-3), 3.84 (s, 3H, Ar-OC<u>H</u>$_3$), 3.71 (d, J=4.8 Hz, 1H, C-2), 3.58-3.52 (m, 2H, C-4), 1.20 (t, J=7.2 Hz, 3H, -OCH$_2$C<u>H</u>$_3$); ^{13}C-NMR (δ in ppm): 195.80 (C-5), 165.16 (C-1), 159.29 (C-4**"**), 135.14 (1"), 132.05 (1'), 131.85, 129.89 (C-3',5'), 129.74, 129.43 (C-2', 6'), 127.85 (4'), 127.52, 127.33 (C-2",6"), 115.79 (-<u>C</u>N), 114.34, 114.21 (C-3'', 5''), 63.02 (CH$_3$<u>C</u>H$_2$O-), 55.27 (Ar-O<u>C</u>H$_3$), 44.27 (C-2), 38.14 (C-4), 26.55 (C-3), 13.91 (<u>C</u>H$_3$CH$_2$O-); MS: m/z 431.06 (100.0%), 429.06 (99.4%), 430.06 (22.9%), 432.06 (22.6%), 433.06 (3.3%); Anal. Found: C, 61.86; H, 6.21; N, 9.45; Calc. for $C_{21}H_{20}BrNO_4$: C, 58.62; H, 4.68; N, 3.26%.

Ethyl 5-(4-chlorophenyl)-2-isocyano-3-(4-methoxyphenyl)-5-oxopentanoate, 4b: Yield 25%; white crystalline solid; mp 162-164°C; R_f value in TLC: 0.45 (chloroform: pet-ether, 3:2); UV (λ_{max} in nm): 260 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O), 228 ($\pi\rightarrow\pi^*$ of C=C-C=O); IR (KBr) (υ_{max} in cm^{-1}): 3008, 2931 (C-H stretching), 2248 (-CN stretching), 1745, 1680 (-C=O stretching), 1588, 1502 (C=C stretching of arom.), 1401 (-CH_3 bending), 1185, 1114 (C-O-C stretching), 875, 816, 789 (=C-H of aromatic ring), 750 (C-Cl stretching); ^{1}H-NMR (δ in ppm): 7.93 (d, J=7.2 Hz, 2H, C-2',6'), 7.51 (d, J=7.2 Hz, 2H, C-3',5'), 7.44 (d, J=7.2 Hz, 2H, C-2",6"), 6.92 (d, J=7.2 Hz, 2H, C-3",5"), 4.27 (q, J=8.8 Hz, 2H, -OC<u>H</u>$_2$CH$_3$), 3.98-3.93 (m, 1H, C-3), 3.79 (s, 3H, Ar-OC<u>H</u>$_3$), 3.73 (d, J=7.2 Hz, 1H, C-2), 3.59-3.52 (m, 2H, C-4), 1.30 (t, J=8.4 Hz, 3H, -OCH$_2$C<u>H</u>$_3$); ^{13}C-NMR (δ in ppm): 196.87 (C-5), 166.25 (C-1), 158.28 (C-4**"**), 138.85 (1''), 130.57, 130.36 (C-3',5'), 134.98 (1'), 128.67, 128.32 (C-2', 6'), 129.88 (4'), 127.86, 127.43 (C-2",6"), 116.83 (-<u>C</u>N), 114.46, 114.28 (C-3'', 5''), 61.32 (CH$_3$<u>C</u>H$_2$O-), 55.89 (Ar-O<u>C</u>H$_3$), 45.63 (C-2), 38.54 (C-4), 26.81 (C-3), 13.27 (<u>C</u>H$_3$CH$_2$O-); MS: m/z 385.11 (100.0%), 387.11 (35.3%), 386.11 (23.5%), 388.11 (7.4%), 389.11 (1.1%); Anal. Found: C, 61.86; H, 6.21; N, 9.45; Calc. for $C_{21}H_{20}ClNO_4$: C, 65.37; H, 5.22; N, 3.63%.

Ethyl 5-(4-chlorophenyl)-2-isocyano-3-(4-methylphenyl)-5-oxopentanoate, 4c: Yield 28%; white crystalline solid; mp 170-172°C; R_f value in TLC: 0.55 (chloroform: pet-ether, 3:2); UV (λ_{max} in nm): 263 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O), 221 ($\pi\rightarrow\pi^*$ of C=C-C=O); IR (KBr) (υ_{max} in cm^{-1}): 3029, 2926 (C-H stretching), 2249 (-CN stretching), 1739, 1660 (-C=O stretching), 1590, 1516 (C=C stretching of arom.), 1402 (-CH_3 bending), 1181 (C-O-C stretching), 892, 813, 790 (=C-H of aromatic ring), 745 (C-Cl stretching); ^{1}H-NMR (δ in ppm): 7.99 (d, J=7.6 Hz, 2H, C-2',6'), 7.48 (d, J=7.6 Hz, 2H, C-3',5'), 7.19-7.13 (m, 4H, C-2",3",5",6"), 4.28 (q, J=7.2 Hz, 2H, -OC<u>H</u>$_2$CH$_3$), 3.99-3.94 (m, 1H, C-3), 2.46 (s, 3H, Ar-C<u>H</u>$_3$), 3.71 (d, J=7.6 Hz, 1H, C-2), 3.61-3.55 (m, 2H, C-4), 1.31 (t, J=7.6 Hz, 3H, -OCH$_2$C<u>H</u>$_3$); ^{13}C-NMR (δ in ppm): 197.65 (C-5), 164.72 (C-1), 138.64 (C-1**"**), 135.83 (C-4'), 131.45 (C-4"), 130.48, 130.26 (C-2', 6'), 128.84, 128.62 (C-3',5'), 134.88 (C-1'), 128.53, 128.26 (C-3'', 5''), 126.63, 126.27 (C-2",6"), 116.87 (-<u>C</u>N), 61.28 (CH$_3$<u>C</u>H$_2$O-), 20.85 (Ar-<u>C</u>H$_3$), 45.78 (C-2), 38.82 (C-4), 23.69 (C-3), 13.43 (<u>C</u>H$_3$CH$_2$O-); MS: m/z 369.11 (100.0%), 371.11 (32%), 370.12 (23.1%), 372.11 (7.4%), 371.12 (3.2%); Anal. Found: C, 61.86; H, 6.21; N, 9.45; Calc. for $C_{21}H_{20}ClNO_3$: C, 68.20; H, 5.45; N, 3.79%.

Ethyl 3,5-bis(4-chlorophenyl)-2-isocyano-5-oxopentanoate, 4d: Yield 23%; white crystalline solid; mp 160-162°C; R_f value in TLC: 0.61 (chloroform: pet-ether, 3:2); UV (λ_{max} in nm): 263 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O), 235 ($\pi\rightarrow\pi^*$ of C=C-C=O); IR (KBr) (υ_{max} in cm^{-1}): 3025, 2935 (C-H stretching), 2245 (-CN stretching), 1740, 1660 (-C=O stretching), 1585, 1515 (C=C stretching of arom.), 1401

(-CH_3 bending), 1185 (C-O-C stretching), 892, 813, 790 (=C-H of aromatic ring), 747 (C-Cl stretching); ^{1}H-NMR (δ in ppm): 7.98 (d, J=7.6 Hz, 2H, C-2',6'), 7.56 (d, J=7.6 Hz, 2H, C-3',5'), 7.40 (d, J=7.6 Hz, 2H, C-3",5"), 7.22 (d, J=7.6 Hz, 2H, C-2",6"), 4.27 (q, J=8.4 Hz, 2H, -$OC\underline{H}_2CH_3$), 3.99-3.93 (m, 1H, C-3), 3.72 (d, J=7.2 Hz, 1H, C-2), 3.58-3.53 (m, 2H, C-4), 1.32 (t, J=8.4 Hz, 3H, -$OCH_2C\underline{H}_3$); ^{13}C-NMR (δ in ppm): 198.45 (C-5), 164.68 (C-1), 138.88 (C-1**"**), 135.64 (C-4'), 134.78 (C-1'), 131.71 (C-4''), 130.66, 130.24 (C-2', 6'), 128.89, 128.78 (C-3', 5'), 128.55, 128.43 (C-3'', 5''), 127.54, 127.32 (C-2",6"), 116.57 (-$\underline{C}N$), 61.56 ($CH_3\underline{C}H_2O$-), 45.68 (C-2), 37.43 (C-4), 26.24 (C-3), 13.36 ($\underline{C}H_3CH_2O$-); MS: m/z 389.06 (100.0%), 391.06 (64.6%), 390.06 (22.3%), 392.06 (14%), 393.05 (10.2%), 394.06 (2.3%), 393.06 (1.9%); Anal. Found: C, 61.86; H, 6.21; N, 9.45; Calc. for $C_{20}H_{17}Cl_2NO_3$: C, 61.55; H, 4.39; N, 3.59%.

III. Results and Discussion

A small amount of crystalline solid of each of the compounds, **3a-d** was dissolved in chloroform and then 2,4-dinitrophenylhydrazine (2,4-DNP) solution was added to it drop wise. A yellow or orange precipitate was formed upon heating which indicated the presence of carbonyl group [>C=O].

The reaction of substituted chalcones, **1a-d** with ethyl cyanoacetate, **2** in presence of sodium ethoxide were conducted to synthesize ethyl 3,5-(disubstituted phenyl)-2-isocyano-5-oxopentanoate, **3a-d** in an analogous way reported previously[35] (**Scheme 1**). The structures of the compounds, **3a-d** were elucidated based on their UV, FT-IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral data and elemental analyses which were comparable to the reported data[36-40].

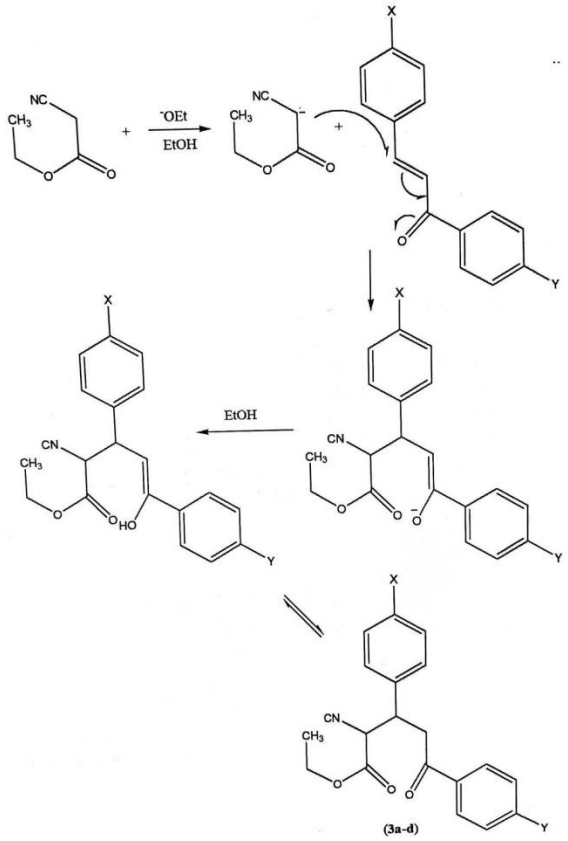
The compounds **3a-d** agree well to the expected λ_{max} values in their UV spectra. The absorption bands in the range 263-257 nm and 235-223 nm are assigned to the π→π* of C=O and C=C of aromatic rings respectively in these compounds.

The IR spectral data of the compounds **3a-d** shows the wave number (ν_{max}), where the functional groups of the compounds have been confirmed by their characteristic peaks. The broad bands in the range (ν_{max}) 3029-2926 cm^{-1} and 2250-2245 cm^{-1} indicates the stretching of C-H and C-N respectively. Non-conjugated C=O stretching were found in between 1745-1660 cm^{-1}. The C=C of aromatic rings were found in the range 1590-1502 cm^{-1}, -CH_3 bending were found in between 1402-1399 cm^{-1} and C-Br/Cl were found in the range 751-590 cm^{-1} for these halogenated aromatic compounds.

In their ^{1}H-NMR of compounds **3a-d**, methylene protons attached to a methyl group at one end and to an electronegative oxygen of ester part at another end gave a quartet at δ 4.28-4.26 ppm in a deshielded region. The methyl groups linked to the above methylene group showed a triplet in a shielded region at δ 1.32-1.20 ppm. In the compounds **3a-d**, the proton at position 3 showed multiplet at δ 4.09-3.93 ppm due to the vicinal coupling with the protons at position 2 and 4, the proton at position 2 showed doublet at δ 3.73-3.71 ppm due to the coupling with the protons at position 3, and the proton at position 4 showed multiplet at δ 3.61-3.52 ppm due to the coupling with the protons at position 3. In the compounds **3a,** and **3b**, the protons of methoxy group attached to aromatic rings showed peak at slightly deshielded region (δ 3.84-3.79) because of the bonded electronegative oxygen atom. In the compound **3c**, the protons of methyl group attached to aromatic ring showed peak at slightly shielded region (δ 2.46). All aromatic protons of these compounds gave peaks in their expected region.

The structure of the compounds, **3a-d,** were further confirmed with their ^{13}C-NMR spectra. In case of the carbonyl carbon (C-5) gave peak at a deshielded region of δ 198.45-195.80 ppm due to of the polarizability of oxygen atom in these compounds. The carbonyl carbon in ester group (C-1) showed signal also at a deshielded region of δ 166.25-164.68 owing to the presence of neighboring electronegative oxygen atom. The chemical shift of carbon of the cyano-group (-CN) were observed at δ 116.87-115.79 ppm. The methylene carbons in an ester group being attached to an oxygen atom are shielded and peak were observed at δ 63.02-61.28 ppm. The methoxy and methyl substituents in benzene ring showed peaks at δ 55.89-55.27 and 20.83 ppm respectively. Moreover, the methyl carbon attached to the ester group showed peak at δ 13.91-13.27 ppm. The carbons at position C-2, C-4 and C-3 showed their expected peak at δ 45.78-44.27, 38.82-37.43 and 26.81-23.69 ppm respectively. All aromatic carbons of these compounds gave peaks in their expected region.

A base catalyzed mechanism of Michael addition as donor component is believed to proceed by the mechanism (**Scheme 2**):



Scheme 2. A plausible mechanism for the synthesis of compounds, **3a-d**.

IV. Conclusion

The process of reacting to acyclic active methylene molecule with a chalcone in the presence of catalytic sodium ethoxide is relatively straightforward, requires no expensive catalysts or high boiling solvents, and is completely environmentally friendly. The synthesized compounds may have a variety of chemical applications and are regarded as useful intermediates in synthetic organic chemistry.

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