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Synthesis of aryl α-keto esters via the rearrangement of aryl cyanohydrin carbonate esters

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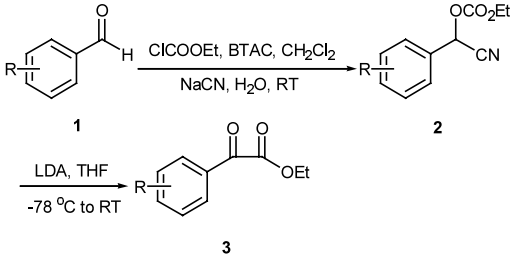
Abstract—A facile synthesis of aryl α-keto esters is reported involving the rearrangement of aryl cyanohydrin carbonate esters induced by the α-carbanion to the nitrile group generated by LDA. However, under similar conditions, an *o*-benzyloxycyanohydrin carbonate ester rearranged via a domino reaction leading to 2-phenylbenzofuran-3-carboxylic acid. © 2003 Elsevier Science Ltd. All rights reserved.

α-Keto acids play a key role in biosynthesis as important substrates and products in the pyridoxal phosphate dependent transaminase enzymatic reaction.[1] Aryl α-keto esters have also been shown to be antisunburn compounds.[2] Interestingly, methyl and butyl 2-(4-methoxyphenyl)-2-oxoacetates have recently been isolated from the hydrophilic extract of the ascidian *Polycarpa aurata*.[3]

Aryl α-keto esters have been described as important intermediates in the synthesis of a variety of oxygenated heterocycles, such as furan derivatives,[4] and in the asymmetric synthesis of biologically active compounds[5] as well as other synthetic compounds.[6] Due to the importance of these α-keto acid derivatives, various methods have been reported for the synthesis of these compounds.[7]

Herein, we present our strategy leading to a short synthesis of aryl α-keto esters **3** via the rearrangement of aromatic cyanohydrin carbonate esters **2**. The aromatic cyanohydrin carbonate esters **2** were prepared by the reaction of aromatic aldehydes **1**, ethyl chloroformate, aq. KCN, and benzyltrimethylammonium chloride (BTAC) in dichloromethane. The reaction is initiated by the attack of cyanide ion on the aldehyde to generate a transient cyanohydrin anion **4** which is then trapped by the chloroformate to give the corresponding cyanohydrin carbonate ester **2** (Scheme 1). Recently, it was found that the preparation of cyanohydrin esters can be effected by the reaction of acylals and KCN in DMSO at room temperature in good to excellent yields.[8] Moreover, when acylals were treated with a mixture of trimethylsilyl cyanide and titanium(IV) chloride, cyanohydrin esters were obtained in good yield from both aliphatic and aromatic acylals.[8]

We found that when the aromatic cyanohydrin carbonate esters **2** were treated with LDA in dry THF at −78°C for an hour and at room temperature for 2 hours, they rearranged smoothly to the aryl α-keto esters **3**. The mechanism of the rearrangement of the aromatic cyanohydrin carbonate ester **2** presumably involved the α-carbanion **5** which could react with the carbonyl function to give the alkoxy epoxide intermedi-



Scheme 1.

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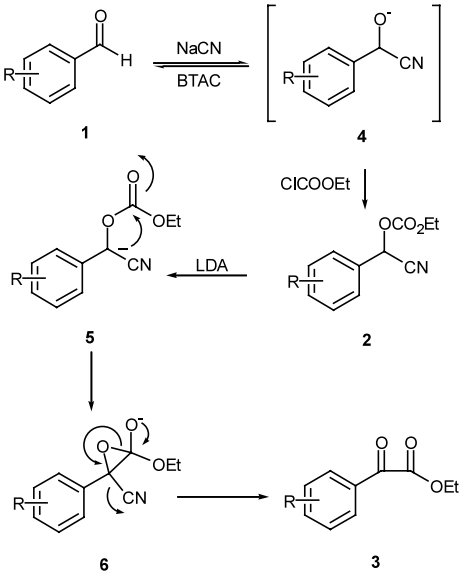
ate **6**. The ring opening of epoxide **6** followed by elimination of cyanide ion would afford keto ester **3** as shown in Scheme 2. The trapping of acyloxy nitrile carbanion with aldehydes and Michael acceptors has been investigated.[9] Using this method, we have successfully converted the aromatic cyanohydrin carbonate esters **2a**–**g** to the corresponding aromatic α-keto esters **3a**–**g** in moderate to good yields as shown in Table 1. Moreover, the methodology can be extended to heteroaromatic systems such as pyridine-2-carboxaldehyde **7**. The 2-ethoxycarbonyloxy-2-(2-pyridyl) acetonitrile **8** was synthesized in 74% yield and smoothly rearranged to ethyl 2-pyridyl-α-oxoacetate **9** in 60% yield as shown in Scheme 3.

The rearrangement of 2-benzyloxyaromatic cyanohydrin ester **2h**, by treatment with LDA in THF at −78°C for an hour and at room temperature overnight, afforded a yellow solid after quenching with saturated ammonium chloride. After recrystallization from ethyl acetate and hexane, yellow crystals were obtained in 65% yield.[12]

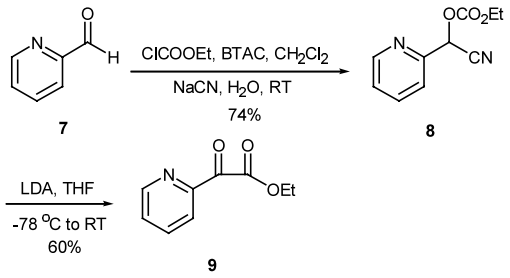


Scheme 2.

Table 1. Yields[a] of aromatic cyanohydrin carbonate esters **2** and aromatic α-keto esters **3**

Entry	Aromatic aldehydes **1**	Yields% **2**[10]	Yields% **3**
1	**a** R = H	85	64
2	**b** R = 2-Me	72	64
3	**c** R = 3-OMe	76	67
4	**d** R = 4-OMe	71	64
5	**e** R = 2,3-di-OMe	77	63
6	**f** R = 3,4-OCH_2O	89	76
7	**g** R = 4-F	74	69
8	**h** R = 2-OCH_2Ph	78[11]	65[b]

[a] Isolated yields.
[b] Yield of compound **11**.

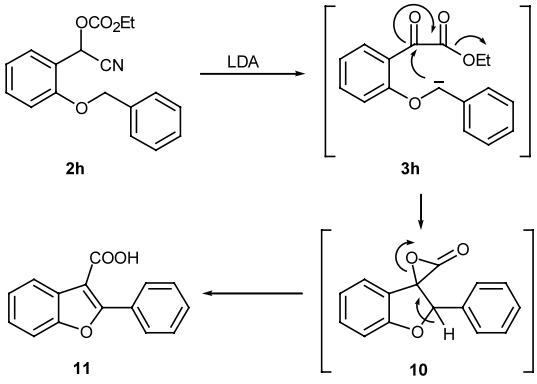


Scheme 3.

The structure of the product obtained under the above conditions was elucidated by interpretation of IR, NMR and MS spectra and it was found that the product was ***not*** the expected glyoxylate **3h**. The structure of the product was deduced to be 2-phenylbenzofuran-3-carboxylic acid **11**.[13] The IR spectrum of **11** showed a broad band at 3216 cm^{-1} (OH of carboxylic group) and a band at 1607 cm^{-1} (C=O of saturated carboxylic group), a carbon signal was observed in the ^{13}C NMR at 173.5. The ethyl group is apparently lost under these non-hydrolytic conditions.

The formation of **11** can be rationalized as first formation of glyoxylate **3h**. Intramolecular cyclization of the benzylic carbanion to the ketone group giving an alkoxide which then could react with the neighboring ester group leading to the spirolactone **10**. The aromatization by ring opening of spirolactone **10** would then give 2-phenylbenzofuran-3-carboxylic acid **11** as shown in Scheme 4.

In conclusion, we have described a new method for the synthesis of α-keto esters involving the rearrangement of aromatic cyanohydrin carbonate esters using LDA. In addition to its simplicity, and efficiency, this procedure provides easy access in moderate to good yields to these useful products. Moreover, the method can be extended as a useful and attractive process for the synthesis of 2-arylbenzofuran derivatives which is under further investigation.



Scheme 4.

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10. *A typical procedure for the preparation of aromatic cyanohydrin carbonate ester*: To a stirred solution of 2-benzyloxy benzaldehyde **1h** (5.3 g, 25.0 mmol), ethyl chloroformate (3.0 g, 27.5 mmol), and benzyltrimethyl ammonium chloride (0.3 g, 1.6 mmol), in dichloromethane (40 mL) cooled in an ice-bath were slowly added a solution of potassium cyanide (2.45 g, 50.0 mmol), in distilled water (40 mL). The mixture was stirred overnight at room temperature. The organic layer was washed with water, saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to give a yellow oil. Purification by distillation under reduced pressure yielded 2-benzyloxyphenyl cyanohydrin carbonate ester **2h** (6.03 g, 78%).
11. Compound **2h**: oil; IR (neat): ν_{max} 1757 (C=O), 1603, 1494, 1455, 1372, 1251, 1008 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J=7.0$ Hz, CH_3), 4.21 (dq, 2H, $J=7.0$ Hz, CH_2), 5.12 (s, 2H, CH_2), 6.65 (s, 1H, CH), 6.97 (dd, 1H, $J=1.0$, 8.0 Hz, ArH), 7.02 (t, 1H, $J=7.4$ Hz, ArH), 7.37 (m, 6H, ArH), 7.59 (dd, 1H, $J=1.8$, 7.6 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 14.0, 61.8, 65.3, 70.3, 112.2, 115.8, 119.7, 121.1, 127.1, 128.0, 128.5, 128.7, 131.9, 135.9, 155.3, 155.7; MS (EI) m/z 311 (M^+, 14), 310 (37), 245 (16), 220 (16), 91 (100). HRMS calcd for $C_{18}H_{17}NO_4$: 311.1158. Found: 311.1159.
12. *A typical procedure for the aromatic cyanohydrin carbonate ester rearrangement*: A solution of lithium diisopropyl amide (LDA) (1.2 mmol) was prepared at 0°C from diisopropyl amine (0.2 mL, 1.2 mmol) in dry THF (3 mL) and 1.3 M *n*-butyllithium (1 mL, 1.2 mmol). After 30 min, the solution was cooled to −78°C and a solution of 2-benzyloxyphenyl cyanohydrin carbonate ester **2h** (0.17 g, 0.5 mmol) in dry THF (2 mL) was added dropwise. The solution was stirred at −78°C for an hour and allowed to reach room temperature overnight. The mixture was quenched with saturated aq. ammonium chloride and extracted with dichloromethane. The organic layer was washed with water, brine, dried (Na_2SO_4), and evaporated to give a yellow solid. Recrystallization using ethyl acetate and hexane yielded 2-phenylbenzofuran-3-carboxylic acid **11** (0.077 g, 65%) as yellowish crystals.
13. Compound **11**: mp 167–168°C; IR (KBr): ν_{max} 3216 (OH), 1607 (C=O), 1562, 1482, 1418, 1288, 1213, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (bs, 1H, OH), 7.51 (m, 5H, ArH), 7.72 (dt, 1H, $J=1.4$, 8.6 Hz, ArH), 8.27 (m, 3H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 118.3, 120.7, 124.5, 125.5, 127.8, 128.6, 130.2, 131.1, 133.6, 138.5, 144.9, 155.5, 173.5; MS (EI) m/z 238 (M^+, 100). HRMS calcd for $C_{15}H_{10}O_3$: 238.0629. Found: 238.0625.