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A regioselective synthesis of aryl substituted arylacetates through ring transformation by ethyl levulinate☆

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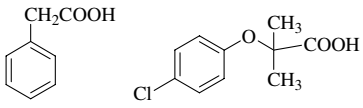
Abstract—A regioselective synthesis of sterically hindered ethyl arylacetates in one step through ring transformation of suitably functionalized 6-aryl-3,4-disubstituted-2*H*-pyran-2-ones with ethyl levulinate at room temperature in excellent yields is described.

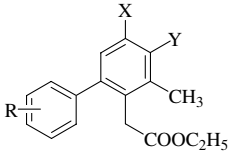
Phenylacetic acid **I** occurs naturally in plasma and forms conjugates with glutamin in human and higher primates.[1,2] The presence of higher levels of phenylacetic acid in plasma reduces[3] the glutamin concentration, essential for the proliferation of cancer cells, and is useful in the treatment of cancer.[4] Clofibric acid **II**, an analog, displays broad spectrum activity including cytostasis and differentiation in various solid tumors.[5–7]

The aliphatic chain of aromatic fatty acids metabolizes repeatedly through β-oxidation[8] while the phenyl ring remains unaffected. Structurally, phenylacetic acid **I** and clofibric acid **II** share an aromatic nucleus and carboxylic acid features and exhibit hypolipidemic properties. Both **I** and **II** also inhibit cholesterol synthesis[9] and protein prenylation in glioblastoma cells.



I

II



III

Alternatively, the esters of phenylacetic acid especially with linalool, are very useful as fragrance compounds[10] in decorative cosmetics, shampoos, toilet-soaps, and also in products such as household cleaners and detergents.[10]

The diverse pharmacological activities of arylacetic acids prompted us to develop a novel route for the synthesis of aryl substituted ethyl arylacetates **III** to explore their therapeutic potential, in particular, by improving their bioavailability and lipophilicity. The synthetic strategies reported in the literature for the synthesis of ethyl arylacetates and analogs are cumbersome and suffer from low yields. These are synthesized by the Wittig reaction of acetophenone and methoxymethylenetriphen- ylphosphonium chloride followed by hydrolysis of the resulting enol ether to the corresponding aldehyde which on further oxidation yields[11] phenylacetic acid **I**. Another method is based on the Friedel–Crafts reaction of chloroacetic acid with benzene using Lewis acids as catalysts.[12] Recently, lanthanide trifluoromethanesulfonates[13a,b] have been employed as catalysts both in organic and aqueous media. Kobayashi et al.[13a] have used $Yb(OTf)_3$ as a catalyst in Friedel–Crafts acylation reactions. Arylacetates have also been synthesized by the reaction of carbon dioxide and various Grignard reagents. The difficulty in this process is the synthesis of moisture sensitive Grignard reagents since they are not available commercially. These compounds are also obtained through acid hydrolysis of arylacetonitriles[14] in good yields. The acids so formed can be esterified[15] by reaction with alcohol using Filtrol-24, Amberlyst-15, zirconium sulfate or heteropolyacids as catalysts.

We report here a very simple and economical regioselective synthesis of highly sterically hindered ethyl arylacetates **III** through ring transformation of 2*H*-pyran-2-one **1** with ethyl levulinate. This is the first report on the synthesis of ethyl arylacetates from 2*H*-pyran-2-ones in

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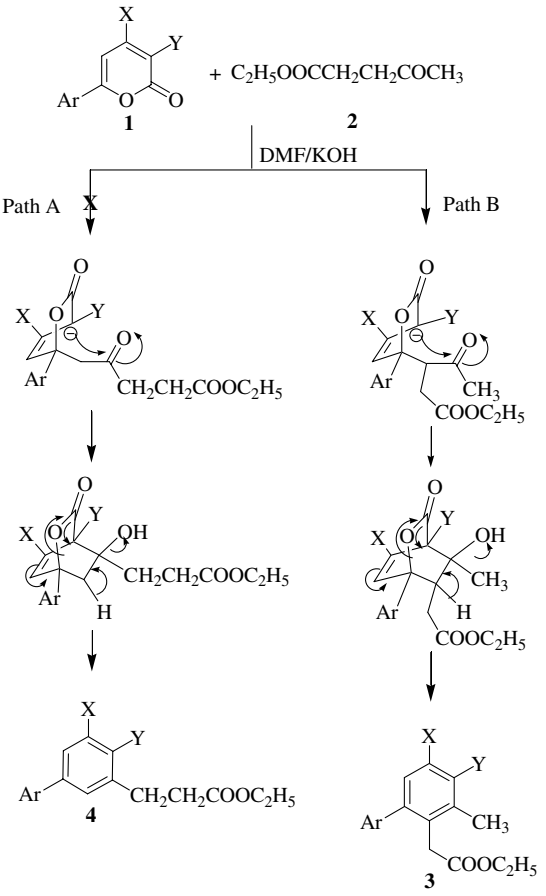

1,3	Ar	X	Y	Yields (%)
a	C_6H_5	SCH_3	$COOCH_3$	79
b	4-FC_6H_4	SCH_3	$COOCH_3$	75
c	4-ClC_6H_4	SCH_3	$COOCH_3$	68
d	4-BrC_6H_4	SCH_3	$COOCH_3$	81
e	4-$CH_3C_6H_4$	SCH_3	$COOCH_3$	81
f	1-naphthyl	SCH_3	$COOCH_3$	71
g	2-thienyl	SCH_3	$COOCH_3$	82
h	4-$CH_3C_6H_4$	SCH_3	CN	60
i	4-ClC_6H_4	piperidin-1-yl	CN	70
j	4-BrC_6H_4	piperidin-1-yl	CN	68
k	4-$CH_3C_6H_4$	piperidin-1-yl	CN	62

Scheme 1.

one-step under very mild reaction conditions. Thus, an equimolar mixture of 2*H*-pyran-2-one **1**, ethyl levulinate **2** and powdered KOH in dry DMF was stirred for 5 h. The progress of the reaction was monitored by TLC until the starting material had completely disappeared. Thereafter, the mixture was poured onto crushed ice with vigorous stirring. The aqueous solution was neutralized with 10% HCl and the resulting precipitate was filtered and purified by silica gel column chromatography. The precursor 2*H*-pyran-2-ones **1a**–**h** were prepared[16] by stirring an equimolar mixture of aryl methyl ketones and methyl 3,3-dimethylthio-2-cyano/carbomethoxyacrylate and KOH in dry DMSO. The 6-aryl-4-piperidin-1-yl-2*H*-pyran-2-one-3-carbonitriles **1i**–**k** were synthesized by refluxing a mixture of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles with piperidine in ethanol for 5 h and isolated as described earlier.[17]

In the structure of 2*H*-pyran-2-one **1**, C-2, C-4, and C-6 are three electrophilic centers in which the latter is highly susceptible to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing substituent at C-3 of the pyran ring. Ethyl levulinate **2**, has two possible sites, C-3, and C-5, for carbanion formation and accordingly two products were expected from this reaction. However, only one product, ethyl 6-aryl-2-methyl-3-cyano/carbomethoxy-4-piperidin-1-yl/methyl-sulfanylphenylacetate **3** was isolated regioselectively in good yields. The isolation of **3** clearly indicates the involvement of a carbanion formed at C-3 of ethyl levulinate **2**, possibly due to the combined inductive effects of the carbonyl and ester groups. The C-5 position in **2** is only influenced by the inductive effect of a carbonyl group which is not as effective as C-3 for generating a carbanion for the reaction to yield ethyl 3-(5-aryl-2,3-disubstituted-phenyl)propionates **4** (Scheme 1). An independent NOE experiment to ascertain the substitution pattern in **3** was carried out. Irradiation of the benzylic protons in **3i** influenced the peak intensity of the methyl as well as the aromatic protons and vice-versa. This confirmed the substitution pattern.

All the synthesized compounds were characterized by spectroscopic and elemental analyses.[18]

Our methodology provides an easy access to the synthesis of highly sterically hindered ethyl arylacetates **3** in one step and in excellent yields without the use of any catalyst with the possibility for introducing substituents at various positions on the phenyl ring. The reaction is very economical and the work-up is very simple.

Acknowledgements

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18. **Representative procedure for the synthesis of ethyl (3-carbomethoxy-2-methyl-4-methylsulfanyl-6-phenyl) phenyl-acetate (3a)**: A mixture of **1a** (1 mmol), ethyl levulinate **2** (1 mmol) and KOH (1.5 mmol) in dry DMF (10 mL) was stirred for 5 h at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl. The precipitate obtained was filtered, washed with water and finally purified by silica gel column chromatography using 1:1 chloroform, hexane as eluent. Yield 79%; viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, $J = 7.08$ Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.43 (s, 3H, SCH_3), 3.53 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 4.11 (q, $J = 7.12$ Hz, 2H, CH_2), 7.10 (s, 1H, ArH), 7.24–7.29 (m, 2H, ArH), 7.38–7.45 (m, 3H, ArH); IR (neat) 1680, 1730 cm^{-1} (CO); MS *m*/*z* 359 (M^++1); $C_{20}H_{22}O_4S$ (358.12): Calcd C, 67.01; H, 6.19. Found: C, 67.21; H, 6.08. Compound (**3b**). Yield 75%; viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, $J = 7.14$ Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.44 (s, 3H, SCH_3), 3.5 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 4.11 (q, $J = 7.12$ Hz, 2H, CH_2), 7.04–7.16 (m, 2H, ArH), 7.21 (s, 1H, ArH), 7.24–7.35 (m, 2H, ArH); IR (neat) 1680, 1726 cm^{-1} (CO); MS *m*/*z* 377 (M^++1); $C_{20}H_{21}FO_4S$ (376.11): Calcd C, 63.81; H, 5.62. Found: C, 64.02; H, 5.75. Compound (**3c**). Yield 68%; viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, $J = 7.12$ Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.44 (s, 3H, SCH_3), 3.50 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 4.12 (q, $J = 7.12$ Hz, 2H, CH_2), 7.06 (s, 1H, ArH), 7.22 (d, $J = 7.96$ Hz, 2H, ArH), 7.38 (d, $J = 7.96$ Hz, 2H, ArH); IR (neat) 1690, 1729 cm^{-1} (CO); MS *m*/*z* 393 (M^++1); $C_{20}H_{21}ClO_4S$ (392.08): Calcd C, 61.14; H, 5.39. Found: C, 61.06; H, 5.54. Compound (**3d**). Yield 81%; viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, $J = 7.12$ Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.43 (s, 3H, SCH_3), 3.5 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 4.12 (q, $J = 7.14$ Hz, 2H, CH_2), 7.06 (s, 1H, ArH), 7.16 (d, $J = 8.44$ Hz, 2H, ArH), 7.53 (d, $J = 8.42$ Hz, 2H, ArH); IR (neat) 1670, 1725 cm^{-1} (CO); MS *m*/*z* 436 (M^+), 438 (M^++2); $C_{20}H_{21}BrO_4S$ (436.03): Calcd C, 54.93; H, 4.84. Found: C, 55.12; H, 4.96. Compound (**3e**). Yield 81%; viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, $J = 7.08$ Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.43 (s, 3H, SCH_3), 3.54 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 4.12 (q, $J = 7.1$ Hz, 2H, CH_2), 7.09 (s, 1H, ArH), 7.13–7.24 (m, 4H, ArH); IR (neat) 1690, 1732 cm^{-1} (CO); MS *m*/*z* 373 (M^++1); $C_{21}H_{24}O_4S$ (372.14): Calcd C, 67.72; H, 6.49. Found: C, 67.56; H, 6.35. Compound (**3f**). Yield 71%; viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (t, $J = 7.12$ Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.44 (s, 3H, SCH_3), 3.56 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 4.10 (q, $J = 7.08$ Hz, 2H, CH_2), 7.19 (s, 1H, ArH), 7.37–7.42 (m, 1H, ArH), 7.49–7.56 (m, 2H, ArH), 7.73–7.75 (m, 1H, ArH), 7.81–7.89 (m, 3H, ArH); IR (neat) 1670, 1731 cm^{-1} (CO); MS *m*/*z* 409 (M^++1); $C_{24}H_{24}O_4S$ (408.14): Calcd C, 70.56; H, 5.92. Found: C, 70.30; H, 6.08. Compound (**3g**). Yield 82%; viscous oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, $J = 7.1$ Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.45 (s, 3H, SCH_3), 3.69 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 4.15 (q, $J = 7.12$ Hz, 2H, CH_2), 7.01–7.09 (m, 2H, ArH), 7.25 (s, 1H, ArH), 7.35–7.38 (m, 1H, ArH); IR (neat) 1680, 1729 cm^{-1} (CO); MS *m*/*z* 365 (M^++1); $C_{18}H_{20}O_4S_2$ (364.08): Calcd C, 59.32; H, 5.53. Found: C, 59.14; H, 5.72. Compound (**3h**). Yield 60%; mp 78–80 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, $J = 7.2$ Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.51 (s, 6H, CH_3, SCH_3), 3.54 (s, 2H, CH_2), 4.14 (q, $J = 7.14$ Hz, 2H, CH_2), 7.00 (s, 1H, ArH), 7.14 (d, $J = 8.12$ Hz, 2H, ArH), 7.23 (d, $J = 8.12$ Hz, 2H, ArH); IR (KBr) 1730 cm^{-1} (CO), 2218 cm^{-1} (CN); MS *m*/*z* 340 (M^++1); $C_{20}H_{21}NO_2S$ (339.13): Calcd C, 70.77; H, 6.29; N, 4.13. Found: C, 70.55; H, 6.14; N, 4.30. Compound (**3i**). Yield 70%; mp 114–116 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, $J = 7.12$ Hz, 3H, CH_3), 1.55–1.63 (m, 2H, CH_2), 1.72–1.83 (m, 4H, CH_2), 2.48 (s, 3H, CH_3), 3.10–3.14 (m, 4H, NCH_2), 3.47 (s, 2H, CH_2), 4.13 (q, $J = 7.12$ Hz, 2H, CH_2), 6.69 (s, 1H, ArH), 7.20 (d, $J = 8.46$ Hz, 2H, ArH), 7.38 (d, $J = 8.48$ Hz, 2H, ArH); IR (KBr) 1736 cm^{-1} (CO), 2211 cm^{-1} (CN); MS *m*/*z* 397 (M^++1); $C_{23}H_{25}ClN_2O_2$ (396.16): Calcd C, 69.60; H, 6.35; N, 7.06. Found: C, 69.49; H, 6.53; N, 7.20. Compound (**3j**). Yield 68%; mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, $J = 7.12$ Hz, 3H, CH_3), 1.59–1.62 (m, 2H, CH_2), 1.74–1.77 (m, 4H, CH_2), 2.48 (s, 3H, CH_3), 3.10–3.14 (m, 4H, NCH_2), 3.46 (s, 2H, CH_2), 4.13 (q, $J = 7.12$ Hz, 2H, CH_2), 6.68 (s, 1H, ArH), 7.14 (d, $J = 8.32$ Hz, 2H, ArH), 7.53 (d, $J = 8.32$ Hz, 2H, ArH); IR (KBr) 1735 cm^{-1} (CO), 2218 cm^{-1} (CN); MS *m*/*z* 440 (M^+), 442 (M^++2); $C_{23}H_{25}BrN_2O_2$ (440.11): Calcd C, 62.59; H, 5.71; N, 6.35. Found: C, 62.52; H, 5.90; N, 6.51. Compound (**3k**). Yield 62%; mp 142–144 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, $J = 7.2$ Hz, 3H, CH_3), 1.57–1.59 (m, 2H, CH_2), 1.75–1.78 (m, 4H, CH_2), 2.40 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.10–3.14 (m, 4H, NCH_2), 3.50 (s, 2H, CH_2), 4.13 (q, $J = 7.1$ Hz, 2H, CH_2), 6.73 (s, 1H, ArH), 7.13 (d, $J = 7.5$ Hz, 2H, ArH), 7.21 (d, $J = 7.5$ Hz, 2H, ArH); IR (KBr) 1734 cm^{-1} (CO), 2216 cm^{-1} (CN); MS *m*/*z* 377 (M^++1); $C_{24}H_{28}N_2O_2$ (376.22): Calcd C, 76.56; H, 7.50; N, 7.44. Found: C, 76.34; H, 7.24; N, 7.30.