A Facile Synthesis of Tetrasubstituted 2,3-Dihydrofuran Derivatives Using Poly(ethylene glycol) as Soluble Support

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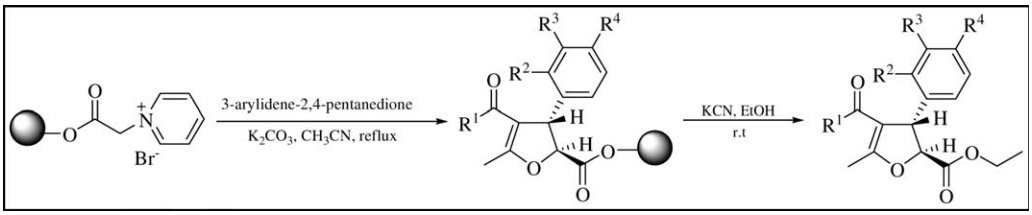

A facile synthesis of tetrasubstitude 2,3-dihydrofurans has been conducted using poly(ethylene glycol) (PEG) as a soluble polymer support. The PEG-supported pyridinium ylides react with 3-arylidene-2,4-pentanedione in the presence of triethylamine (TEA) via conjugate addition to form PEG-supported dihydrofuran derivatives, being cleaved by 1% KCN/EtOH to afford *trans*-tetrasubstitude-2,3-dihydrofurans, varying from good to excellent yields.

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INTRODUCTION

Dihydrofurans are the most important heterocycles not only because of their biological activities [1] but also to potential usefulness as synthetic intermediates, for example, they are precursors of furans by oxidation. Searching for new and efficient methods for their synthesis is always an area of synthetic interest. With a number of methods available, though, the synthesis of dihydrofurans using polymer as support has never been reported. Our laboratory has accumulated abundant experience in soluble polymer supported synthesis [2] and has successfully synthesized indolizines using poly(ethylene glycol) (PEG)-supported pyridinium ylides [3]. Based on our previous work, herein we report the facile synthesis of tetrasubstituted dihydrofuran deriatives via the reaction of 3-arylidene-2,4-pentanedione analogues **3** [4] with PEG-supported pyridinium ylides 2 (Scheme 1).

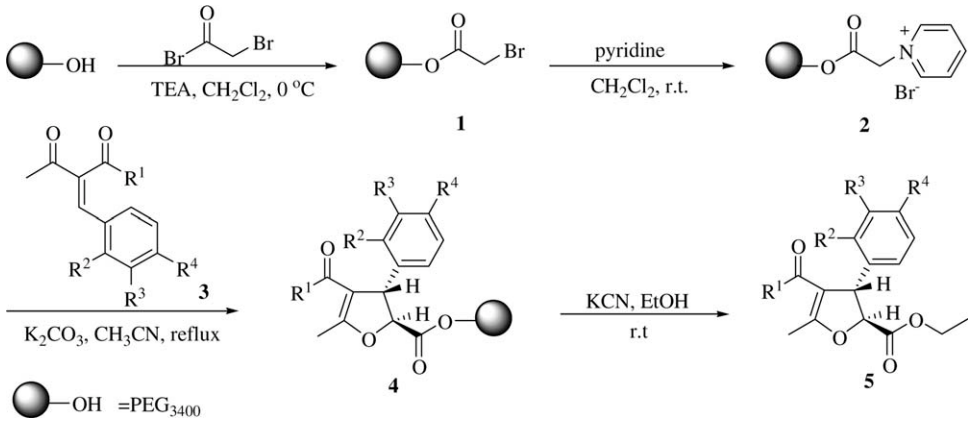
RESULTS AND DISCUSSION

As shown in Scheme 1, PEG_{3400} was first treated by two equivalent bromoacetyl bromide with equimultiple triethylamine (TEA) as base in dry dichloromethane at 0°C overnight to form **1**. The IR spectroscopy of **1** exhibits characteristic C=O absorption band at 1750 cm^{-1} with the disappearance of the O—H absorption at 3448 cm^{-1}. After purification and vacuum drying, **1** was reacted with pyridine overnight in dry dichloromethane to afford PEG-supported pyridinium ylides **2**. The ^1H NMR spectroscopy of **2** shows a strong signal of the pyridine protons at δ 9.46, 8.62, and 8.20. The ylides reacted with 1.5 equivalent of 3-arylidene-2,4-pentanedione **3** at refluxing temperature via conjugate addition in dry acetonitrile using K_2CO_3 as a base, and **4** was obtained as brown powder in excellent yields. Finally, the 2,3-dihydrofuran **5** was cleaved from **4** by treating **4** with 1% KCN in dry ethanol solution at r.t. over night in 80–93% yields.

The earlier papers reported that using ylides react at 0°C or even −78°C gives birth to cyclopropane and dihydrofuran products, but if choosing higher temperature only dihydrofuran was obtained [5]. Probably because of the raise of temperature, the less stable carbon anionic intermediate **A** would transform to oxygen anionic intermediate **B**, thus resulting in the contrast of their chemselectivity; the higher the temperature is chosen the better chemselectivity is gained. Their common mechanism is shown in Scheme 2.

During the study of the mechanism, we envision that we could use PEG-supported pyridinium ylide to synthesize 2,3-dihydrofuran derivatives in acetonitrile at refluxing temperature. Indeed, we do obtain 2,3-dihydrofuran as the only product in our route. The stereochemistry of 5a is assigned from a combination of its COSY spectra in which a *trans*-geometry between the 4 and 5-

Scheme 1



positions is observed ($J = 4.2$ Hz) [6]. A plausible reaction mechanism is shown in Scheme 3. As the reaction conducts at refluxing temperature, the carbon anionic intermediate I is so instable that it would be transformed to oxygen anionic intermediate II, so no cyclopropane derives from a three-membered ring could be detected. There are two possible scenarios when the enolate oxygen attacks C_2 from the backside of leaving group (Py^+) such as III and IV. To be largely affected by the steric hindrance (Ar and PEG-OCO), especially by the group of PEG-OCO, IV is so instable as to be insignificant, thus *trans*-2,3-dihydrofuran is the only product detected in our route (Scheme 3).

Initial attempts worked perfectly with ethyl-2-(4-chlorobenzylidene)-3-oxobuancate **3a** and PEG-supported pyridinium ylieds **2** in acetonitrile at refluxing temperature with K_2CO_3 as base and *trans*-5-methyl-3-(3-nitrophenyl)-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester **5e** was formed in 82% yield (based on the loading capacity of PEG). To probe into the generality of this finding, we extend the investigation to a number of substrates, of which 17 products have never been reported. The results are summarized in Table 1.

This method has a number of advantages including high yields, simple purification, and absence of competing side reactions such as C-cyclization, which are all based on the features of PEG supported synthesis [7]: (a) in each step, the excess low molecular regents are used to promote the balance movement to the product direction so as to obtain high yields; (b) the PEG supported group provides huge steric hindrance to restrict enolate oxygen to attack carbon at a certain direction, thus leading to high stereoselectivity; and (c) PEG-bound products can be conveniently recrystalled in cold ethyl ether, and the by-products are removed by simple filtration, which simplifies the purification a lot.

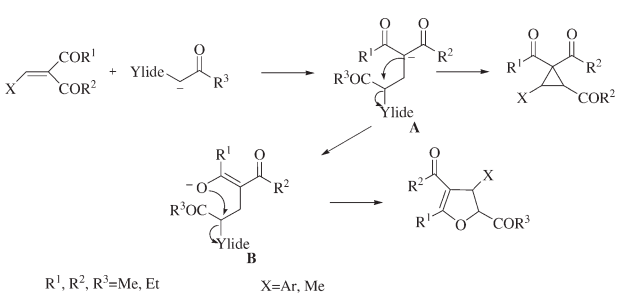
In conclusion, we have successfully synthesized 22 *trans*-tetrasubstituted 2,3-dihydrofuran derivatives via the reaction of 3-arylidene-2,4-pentanedione with PEG-supported pyridinium ylides in high yields, simple purification and 17 products have never been reported.

EXPERIMENTAL

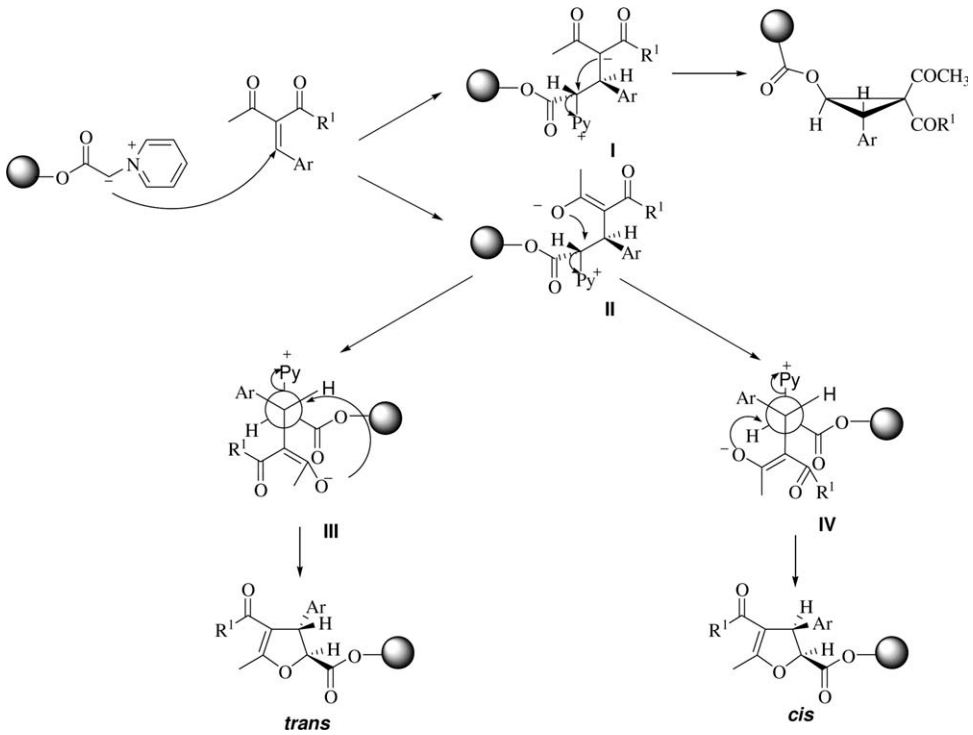
All organic solvents were dried by standard methods. PEG_{3400} (Aldrich, 3015–3685) and PEG-supported compounds were melted in vacuum at 80°C for about 30 min before use, to remove any trace of moisture. Melting points were measured by a X-6 digital melting point apparatus and uncorrected. IR spectra were recorded in an IR-Spectrum One spectrometer (Perin Elmer), using NaCl pellets. Mass spectra were recorded on Finnigan LCQ DUO MS system. ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded in a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS (0.03%) as internal standard.

Preparation of PEG-supported pyridinium ylides 2. A solution of bromoacetyl bromide (1.02 mL, 11.76 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a solution of PEG_{3400} (10.0 g, 5.88 mmol OH) and Et_3N (1.65 mL, 11.76 mmol) in dry CH_2Cl_2 (30 mL) at 0°C and stirred at r.t. overnight. The mixture was washed with H_2O to remove $Et_3N{\cdot}HBr$, dried over Na_2SO_4 and concentrated. After precipitation with cold Et_2O, washing with cold Et_2O and drying under vacuum, a light yellow solid **1** was obtained. Pyridine (0.94 mL, 11.76 mmol) was added to a solution of **1** in dry CH_2Cl_2 (30 mL) and stirred at r.t overnight. After precipitation from cold Et_2O, the suspension was filtered and washed with cold Et_2O to obtain solid **2** (11.0 g, 98%). TLC (EA:PE =

Scheme 2



Scheme 3



1:4) showed that the solid was free from any low molecular reactants and by-products. IR (NaCl): 3057, 2882, 1751, 1147, 1114, 730 cm^{-1}. ^1H NMR (600 MHz): δ = 9.46 (d, 2H, *J* = 4.2 Hz, α-pyridine), 8.62 (t, 1H, *J* = 6.4 Hz, γ-pyridine), 8.20 (t, 2H, *J* = 6.0 Hz, β-pyridine), 6.18 (s, 2H, —CH_2COO—), 3.64–3.51 (m, 4nH, —$O(CH_2CH_2O)n$—).

Typical procedures for preparation of 2,3-dihydrofurans 5. A mixture of PEG-supported pyridinium ylides **2** (2.3 mmol), 3-benzylidene-2,4-pentanedione (3.44 mmol), and K_2CO_3 (3.44 mmol) in CH_3CN (20 mL) was refluxed for 12 h to form **4**. After the solvent was evaporated under vacuum, the residue was added to CH_2Cl_2 (5 mL) and recrystalled in cold Et_2O. Filtering the precipitation and being washed by the cold Et_2O until no low molecular reactants and by-product, which were detected by the TLC (EA:PE = 1:4). Product **4** was treated with 1% solution of KCN in EtOH (30 mL) and stirred at r.t overnight, evaporated EtOH and precipitated with cold Et_2O to obtain the crude products, which were purified by column chromatography on silica gel (EA:PE = 1:4) to afford the pure **5**.

Trans-4-acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Aa) oil. IR (NaCl): 2956, 1759, 1702, 1651, 1462 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.313 (d, 2H, *J* = 8.4 Hz, ArH), 7.200 (d, 2H, *J* = 8.4 Hz, ArH), 4.782 (d, 1H, *J* = 4.2 Hz, OCH), 4.495 (d, 1H, *J* = 4.6 Hz, CH), 4.206 (m, 2H, OCH_2), 2.435 (s, 3H, CH_3), 1.994 (s, 3H, CH_3), 1.456 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.505, 168.870, 164.219, 140.222, 132.476, 130.104 (2C), 129.896 (2C), 105.957, 85.848, 62.202, 59.862, 29.670, 14.132, 13.893, 13.528. MS: *m*/*z* = 339.13 ($M^+ + 1$).

Trans-4-acetyl-3-(4-bromophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ab) oil. IR (NaCl): 2884, 1746, 1620, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.290 (d, 2H, *J* = 8.4 Hz, ArH), 7.173 (d, 2H, *J* = 8.4 Hz, ArH), 4.770 (d, 1H, *J* = 5.4 Hz, OCH), 4.394 (d, 1H, *J* = 3.6 Hz, CH), 4.280 (m, 2H, OCH_2), 4.023 (m, 2H, OCH_2), 2.397 (s, 3H, CH_3), 1.326 (t, 3H, CH_3), 1.095 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.413, 168.882, 164.307, 140.194, 132.430 (2C), 131.876 (2C), 121.782, 106.293, 85.814, 62.255, 59.971, 29.588, 14.076, 13.985, 13.859. MS: *m*/*z* = 383.02 ($M^+ + 1$).

Trans-4-acetyl-3-(4-cyanophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ac) oil. IR (NaCl): 2883, 1753, 1627, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.569 (d, 2H, *J* = 7.8 Hz, ArH), 7.287 (d, 2H, *J* = 7.8 Hz, ArH), 5.338 (d, 1H, *J* = 5.4 Hz, OCH), 4.646 (d, 1H, *J* = 3.6 Hz, CH), 4.007 (m, 2H, OCH_2), 3.796 (m, 2H, OCH_2), 2.397 (s, 3H, CH_3), 1.326 (t, 3H, CH_3), 1.023 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.843, 168.232, 164.117, 146.262, 133.945 (2C), 130.554 (2C), 117.852, 110.967, 105.729, 85.608, 61.940, 59.774, 29.637, 14.081, 13.953, 13.452. MS: *m*/*z* = 330.16 ($M^+ + 1$).

Trans-4-acetyl-3-(4-nitrophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ad) oil. IR (NaCl): 2885, 1750, 1629, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 8.156 (d, 2H, *J* = 8.4 Hz, ArH), 7.358 (d, 2H, *J* = 7.8 Hz, ArH), 5.244 (d, 1H, *J* = 4.2 Hz, OCH), 4.683 (d, 1H, *J* = 4.8 Hz, CH), 4.116 (m, 2H, OCH_2), 3.827 (s, 3H, CH_3), 2.481 (s, 3H, CH_3), 1.251 (t, 3H, CH_3),1.024 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.145, 168.427, 163.536, 146.893, 145.615, 128.774 (2C), 121.309 (2C), 105.697, 85.517, 61.823, 59.633, 29.621, 14.248, 13.978, 13.863. MS: *m*/*z* = 350.15 ($M^+ + 1$).

Trans-4-acetyl-3-(3-nitrophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ae) oil. IR (NaCl): 2957, 1761, 1700, 1651, 1532 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ

Table 1

Synthesis of 2,3-dihydrofurans using PEG-supported pyridin ylide.

Entry	R^1	R^2	R^3	R^4	Yield (%)[a]
5Aa	OEt	H	H	Cl	82
5Ab	OEt	H	H	Br	85
5Ac	OEt	H	H	CN	87
5Ad	OEt	H	H	NO_2	80
5Ae	OEt	H	NO_2	H	90
5Af	OEt	NO_2	H	H	81
5Ag	OEt	H	H	OCH_3	89
5Ah	OEt	OCH_3	OCH_3	H	85
5Ai	OEt	H	H	$N(CH_3)_2$	90
5Aj	OEt	Cl	H	Cl	83
5Ak	OEt	H	H	OH	80
5Ba [5b]	CH_3	H	H	Cl	84
5Bb [5b]	CH_3	H	H	Br	86
5Bc	CH_3	H	H	CN	88
5Bd [5b]	CH_3	H	H	NO_2	87
5Be	CH_3	H	NO_2	H	93
5Bf	CH_3	NO_2	H	H	85
5Bg	CH_3	H	H	OCH_3	92
5Bh	CH_3	OCH_3	OCH_3	H	87
5Bi	CH_3	H	H	$N(CH_3)_2$	89
5Bj [5b]	CH_3	Cl	H	Cl	84
5Bk	CH_3	H	H	OH	80

[a] Based on the loading capacity of PEG.

= 8.058 (m, 1H, ArH), 7.535–7.437 (m, 2H, ArH), 4.786 (d, 1H, J = 5.4 Hz, OCH), 4.488 (d, 1H, J = 4.2 Hz, CH), 4.208 (m, 2H, OCH_2), 3.954 (m, 2H, OCH_2), 2.355 (s, 3H, CH_3), 1.308 (s, 3H, CH_3), 1.022 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.945, 168.848, 163.609, 149.223, 136.138, 133.547, 128.841, 128.143, 124.198, 105.840, 86.077, 61.985, 59.682, 29.543, 14.108, 13.962, 13.439. MS: m/z = 350.10 ($M^+ + 1$).

Trans-4-acetyl-3-(2-nitrophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Af) oil. IR (NaCl): 2925, 1759, 1651, 1462 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.786 (d, 1H, J = 7.8 Hz, ArH), 7.518 (m, 1H, ArH), 7.328 (t, 2H, ArH), 5.062 (d, 1H, J = 4.2 Hz, OCH), 4.809 (d, 1H, J = 4.8 Hz, CH), 4.249 (m, 2H, OCH_2), 3.893 (m, 2H, OCH_2), 2.350 (s, 3H, CH_3), 1.285 (s, 3H, CH_3), 0.911 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.635, 169.948, 164.202, 149.163, 136.793, 132.803, 129.837, 128.153, 124.289, 105.715, 85.407, 62.068, 59.712, 29.630, 14.076, 13.996, 13.954. MS: m/z = 350.16 ($M^+ + 1$).

Trans-4-acetyl-3-(4-methoxyphenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ag) oil. IR (NaCl): 2880, 1751, 1636, 1467 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.018 (d, 2H, J = 8.4 Hz, ArH), 6.878 (d, 2H, J = 8.4 Hz, ArH), 4.799 (d, 1H, J = 4.8 Hz, OCH), 4.406 (d, 1H, J = 4.8 Hz, CH), 4.269 (m, 2H, OCH_2), 4.018 (m, 2H, OCH_2), 2.384 (s, 3H, CH_3), 1.323 (t, 3H, CH_3), 1.096 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.022, 169.923, 164.879, 159.743, 133.320, 128.845 (2C), 114.289 (2C), 105.729, 85.407, 62.068, 59.663, 56.014, 29.630, 14.076, 13.996, 13.954. MS: m/z = 335.16 ($M^+ + 1$).

Trans-3-(2,3-dimethoxyphenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ah) oil. IR (NaCl): 2884, 1746, 1620, 1467 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.032 (t, 1H, ArH), 6.851 (d, 1H, J = 7.2 Hz, ArH), 6.680 (d, 1H, J = 7.8 Hz, ArH), 4.919 (d, 1H, J = 4.2 Hz, OCH), 4.618 (d, 1H, J = 3.6 Hz, CH), 4.369 (m, 2H, OCH_2), 4.172 (m, 2H, OCH_2), 3.883 (s, 6H, OCH_3), 2.419 (s, 3H, CH_3), 1.448 (t, 3H, CH_3), 1.263 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.104, 169.945, 164.862, 150.739, 150.022, 127.242, 122.853, 121.197, 112.827, 105.723, 85.418, 62.053, 59.657, 56.542, 56.012, 29.629, 14.202, 13.988, 13.945. MS: m/z = 365.20 ($M^+ + 1$).

Trans-4-acetyl-3-(2,4-dichlorophenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Aj) oil. IR (NaCl): 2885, 1750, 1629, 1467 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.394 (d, 1H, J = 8.4 Hz, ArH), 7.264 (d, 1H, J = 8.4 Hz m, ArH), 7.258–7.240 (m, 1H), 5.114 (d, 1H, J = 4.2 Hz, OCH), 4.703 (d, 1H, J = 4.8 Hz, CH), 4.244 (m, 2H, OCH_2), 4.013 (m, 2H, OCH_2), 2.463 (s, 3H, CH_3), 2.068 (s, 3H, CH_3), 1.216 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.324, 168.998, 163.545, 137.132, 136.454, 134.317, 130.623, 130.304, 126.492, 105.731, 85.772, 62.104, 59.672, 29.534, 14.088, 13.831, 13.456. MS: m/z = 373.09 ($M^+ + 1$).

Trans-4-acetyl-3-(4-hydroxyphenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ak) oil. IR (NaCl): 2883, 1750, 1637, 1467 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.099 (s, 1H, OH), 7.469 (d, 2H, J = 8.4 Hz, ArH), 6.922 (d, 1H, J = 8.4 Hz, ArH), 4.843 (d, 1H, J = 4.2 Hz, OCH), 4.307 (d, 1H, J = 4.8 Hz, CH), 4.309 (m, 2H, OCH_2), 4.127 (m, 2H, OCH_2), 2.382 (s, 3H, CH_3), 1.954 (s, 3H, CH_3), 1.278 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.582, 168.763, 163.425, 156.753, 133.406, 130.287 (2C), 116.848 (2C), 105.724, 85.788, 62.146, 59.672, 29.630, 14.071, 13.835, 13.452. MS: m/z = 321.19 ($M^+ + 1$).

Trans-4-acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Ba) oil. IR (NaCl): 2957, 1760, 1704, 1651, 1459 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.401 (d, 2H, J = 9.0 Hz, ArH), 7.374 (d, 2H, J = 9.0 Hz, ArH), 4.729 (d, 1H, J = 4.8 Hz, OCH), 4.474 (d, 1H, J = 4.2 Hz, CH), 4.310 (m, 2H, OCH_2), 2.428 (s, 3H, CH_3), 1.994 (s, 3H, CH_3), 1.294 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.511, 168.864, 164.230, 140.217, 132.465, 130.109 (2C), 129.882 (2C), 105.943, 85.826, 62.213, 29.672, 14.162, 13.877, 13.519 MS: m/z = 309.11 ($M^+ + 1$).

Trans-4-acetyl-3-(4-bromophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bb) oil. IR (NaCl): 2884, 1742, 1621, 1460 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.290 (d, 2H, J = 8.4 Hz, ArH), 7.173 (d, 2H, J = 8.4 Hz, ArH), 4.770 (d, 1H, J = 5.4 Hz, OCH), 4.394 (d, 1H, J = 3.6 Hz, CH), 4.280 (m, 2H, OCH_2), 4.023 (m, 2H, OCH_2), 2.397 (s, 3H, CH_3), 1.326 (t, 3H, CH_3), 1.095 (t, 3H, CH_3),^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.405, 168.874, 164.311, 140.186, 132.418 (2C), 131.856 (2C), 121.796, 106.185, 85.801, 62.203, 29.463, 14.067, 13.993, 13.835. MS: m/z = 353.07 ($M^+ + 1$).

Trans-4-acetyl-3-(4-cyanophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bc) oil. IR (NaCl): 2884, 1752, 1623, 1459 cm^{-1}, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.687 (d, 2H, J = 3.6 Hz, ArH), 7.555 (d, 2H, J = 4.8 Hz, ArH), 5.016 (d, 1H, J = 4.8 Hz, OCH), 4.453 (d, 1H, J = 4.8 Hz, CH), 4.076 (m, 2H, OCH_2), 2.423 (s, 3H, CH_3), 2.398 (s, 3H, CH_3), 1.265 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.852, 168.229, 164.110, 146.258, 133.931 (2C), 130.567 (2C), 117.844, 110.960, 105.718, 85.614, 61.943, 29.626, 14.125, 13.948, 13.433. MS: m/z = 302.14 ($M^+ + 1$).

Tans-4-acetyl-3-(4-nitrohenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bd) oil. IR (NaCl): 2883, 1748, 1630, 1478 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 8.211 (d, 2H, *J* = 4.2 Hz, ArH), 7.424 (d, 2H, *J* = 8.4 Hz, ArH), 4.761 (d, 1H, *J* = 4.8 Hz, OCH), 4.609 (d, 1H, *J* = 4.2 Hz, CH), 4.308 (m, 2H, OCH_2), 2.468 (s, 3H, CH_3), 2.103 (s, 3H, CH_3), 1.251 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.138, 168.414, 163.552, 146.872, 145.609, 128.772 (2C), 121.319 (2C), 105.693, 85.523, 61.835, 29.624, 14.236, 13.994, 13.842. MS: *m/z* = 320.14 (M^+ + 1).

Trans-4-acetyl-3-(3-nitrophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Be) oil. IR (NaCl): 2935, 1757, 1690, 1628, 1521 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.899 (d, 1H, *J* = 7.8 Hz, ArH), 7.609 (m, 1H, ArH), 7.352 (d, 1H, *J* = 7.2 Hz, ArH), 5.223 (d, 1H, *J* = 5.4 Hz, OCH), 4.853 (d, 1H, *J* = 4.2 Hz, CH), 4.402 (m, 2H, OCH_2), 2.4485 (s, 3H, CH_3), 2.020 (s, 3H, CH_3), 1.022 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.932, 168.824, 163.679, 149.235, 136.131, 133.459, 128.856, 128.258, 124.183, 105.833, 86.102, 61.973, 29.536, 14.112, 13.953, 13.538. MS: *m/z* = 320.13 (M^+ + 1).

Trans-4-acetyl-3-(2-nitrophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bf) oil. IR (NaCl): 2913, 1762, 1651, 1469 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.899 (d, 1H, *J* = 7.8 Hz, ArH), 7.606 (t, 1H, ArH), 7.448 (t, 1H, ArH), 7.352 (d, 1H, *J* = 7.8 Hz, ArH), 5.234 (d, 1H, *J* = 3.6 Hz, OCH), 4.792 (d, 1H, *J* = 5.4 Hz, CH), 4.309 (m, 2H, OCH_2), 2.456 (s, 3H, CH_3), 2.015 (s, 3H, CH_3), 1.025 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.648, 169.932, 164.132, 149.153, 136.643, 133.311, 128.894, 128.073, 124.289, 105.715, 85.407, 62.068, 29.630, 14.076, 13.996, 13.954. MS: *m/z* = 320.09 (M^+ + 1).

Trans-4-acetyl-3-(4-methoxyphenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bg) oil. IR (NaCl): 2882, 1753, 1639, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.024 (d, 2H, *J* = 8.4 Hz, ArH), 6.873 (d, 2H, *J* = 8.4 Hz, ArH), 4.798 (d, 1H, *J* = 5.4 Hz, OCH), 4.339 (d, 1H, *J* = 5.4 Hz, CH), 4.010 (m, 2H, OCH_2), 3.849 (s, 3H, OCH_3), 2.411 (s, 3H, CH_3), 1.319 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.102, 169.943, 164.867, 159.739, 133.321, 128.842 (2C), 114.287 (2C), 105.714, 85.401, 62.053, 59.657, 56.012, 29.618, 14.102, 13.982, 13.946. MS: *m/z* = 305.15 (M^+ + 1).

Trans-3-(2,3-dimethoxyphenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bh) oil. IR (NaCl): 2885, 1750, 1631, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.805 (s, 1H, ArH), 7.042-6.977 (m, 2H, ArH), 4.609 (d, 1H, *J* = 5.4 Hz, OCH), 4.353 (d, 1H, *J* = 5.2 Hz, CH), 4.189 (m, 2H, OCH_2), 3.896 (s, 6H, OCH_3), 2.886 (s, 3H, CH_3), 2.440 (s, 3H, CH_3), 1.263 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.105, 169.943, 164.860, 150.734, 150.018, 127.238, 122.847, 121.186, 112.833, 105.719, 85.408, 62.048, 56.540, 56.018, 29.623, 14.210, 13.978, 13.953. MS: *m/z* = 335.17 (M^+ + 1).

Trans-4-acetyl-3-(4-(dimethylamino)phenyl)-5-methyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (5Ai) oil. IR (NaCl): 2883, 1753, 1627, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.310 (d, 2H, *J* = 8.4 Hz, ArH), 6.627 (d, 2H, *J* = 8.4 Hz, ArH), 4.793 (d, 1H, *J* = 4.8 Hz, OCH), 4.475 (d, 1H, *J* = 4.2 Hz, CH), 4.275 (m, 2H, OCH_2), 4.063 (m, 2H, OCH_2), 3.033 (s, 6H, $N(CH_3)_2$), 2.407 (s, 3H, CH_3), 1.305 (s, 3H, CH_3), 1.170 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.875, 168.843, 164.324, 146.738, 130.218, 129.236 (2C), 115.833 (2C), 106.119, 85.402, 62.029, 41.309 (2C), 29.425, 14.201, 13.977, 13.946. MS: *m/z* = 348.12 (M^+ + 1).

Trans-4-acetyl-3-(4-(dimethylamino)phenyl-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bi) oil. IR (NaCl): 2884, 1752, 1628, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.307(d, 2H, *J* = 10.8 Hz, ArH), 6.662 (d, 2H, *J* = 8.4 Hz, ArH), 4.778 (d, 1H, *J* = 4.8 Hz, OCH), 4.425 (d, 1H, *J* = 4.2 Hz, CH), 4.364 (m, 2H, OCH_2), 3.046 (s, 6H, $N(CH_3)_2$), 2.413 (s, 3H, CH_3), 2.387 (s, 3H, CH_3), 1.317 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.870, 168.838, 164.322, 146.730, 130.222, 129.234 (2C), 115.829 (2C), 106.121, 85.389, 41.306 (2C), 29.414, 14.322, 13.984, 13.953. MS: *m/z* = 318.21 (M^+ + 1).

Trans-4-acetyl-3-(2,4-dichlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bj) IR (NaCl): 2883, 1748, 1629, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 7.390 (d, 1H, *J* = 1.8 Hz, ArH), 7.254 (m, 1H, ArH), 7.095 (d, 1H, *J* = 8.4 Hz), 5.014 (d, 1H, *J* = 4.2 Hz, OCH), 4.699 (d, 1H, *J* = 4.8 Hz, CH), 4.292 (m, 2H, OCH_2), 2.444 (s, 3H, CH_3), 1.986 (s, 3H, CH_3), 1.299 (t, 3H, CH_3),^{13}C NMR (150MHz, $CDCl_3$): δ = 169.321, 168.977, 163.541, 137.127, 136.439, 134.306, 130.640, 130.287, 126.488, 105.716, 85.759, 62.113, 29.530, 14.064, 13.845, 13.458. MS: *m/z* = 343.01 (M^+ + 1).

Trans-4-acetyl-3-(4-hydroxyphenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (5Bk) oil. IR (NaCl): 2883, 1755, 1628, 1467 cm^{-1}, ^1H NMR (600 MHz, $CDCl_3$): δ = 8.807 (s, 1H, OH), 7.321 (d, 2H, *J* = 8.4 Hz, ArH), 7.193 (d, 1H, *J* = 8.4 Hz, ArH), 4.767 (d, 1H, *J* = 4.8 Hz, OCH), 4.435 (d, 1H, *J* = 5.4 Hz, CH), 4.315 (m, 2H, OCH_2), 2.431 (s, 3H, CH_3), 2.052 (s, 3H, CH_3), 1.278 (t, 3H, CH_3), ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.580, 168.758, 163.422, 156.749, 133.401, 130.285 (2C), 116.832 (2C), 105.715, 85.764, 62.108, 59.712, 29.639, 14.063, 13.828, 13.457. MS: *m/z* = 291.09 (M^+ + 1).

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REFERENCES AND NOTES

[1] (a) Hudlicky, T.; Lovelace, T. C. Synth Commun 1990, 20, 1721; (b) Dulere, J. P.; Baret, N.; Rodriguez, J. J Chem Soc Chem Commun 1994, 303.

[2] (a) Zhang, H.-Q.; Yang, G.-C.; Chen, J-.N.; Chen, Z.-X. Synthesis 2004, 18, 3055; (b) Behrendt, J.-M.; Bala, K.; Golding, P. Tetrahedron Lett 2005, 46, 643; (c) Yue, G.-Z.; Chen, Z.-X.; Yang, G.-C. J Heterocycl Chem 2006, 43, 781; (c) Yue, G.-Z.; Chen, Z.-X. Bioorg Med Chem Lett 2005, 15, 453; (d) Huang, Y.-L.; Lu, C.-F.; Chen, Z.-X.; Yang, G.-C. J Heterocycl Chem 2007, 44, 1421; (e) Xiang, F.-Y.; Zhang, S.-B.; Lu, C.-F.; Chen, Z.-X.; Yang, G.-C. Synth Commun 2008, 38, 953; (f) Xie, H.-W.; Lu, C.-F.; Chen, Z.-X.; Yang, G.-C. Synthesis 2009, 2, 205.

[3] Chen, Z.-X.; Yue, G.-Z. Synlett 2004, 1231.

[4] (a) Antonioletti, R.; Bovicelli, P.; Malancoha, S. Tetrahedron 2002, 58, 589; (b) Bartoli, G.; Bosco, M.; Carlone, A.; Daplozzo,

R.; Galzerano, P.; Melchiorre, P.; Sambri, L. Tetrahedron 2008, 49, 2555.

[5] (a) Payne, G.-B. J Org Chem 1967, 11, 3351; (b) Chuang, C.-P.; Tsai, A. I. Synthesis 2006, 4, 675; (c) Cao, W.-G.; Chen, G.-D.; Chen, J.; Chen, R.-Q. Synth Commun 2005, 35, 527.

[6] Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K. I.; Shioiri, T. Tetrahedron 1998, 39, 9739.

[7] (a) Far, A. R.; Tidwell, T. T. J Org Chem 1998, 63, 8636; (b) Pan, P.-C.; Sun, C.-M. Tetrahedron Lett 1998, 39, 9055; (c) Benaglia, M.; Cinquini, M.; Cozzi, F. Tetrahedron Lett 1999, 40, 2019; (d) Lopea-Pelegrin, J. A.; Wentworth, P.; Sieber, F.; Metz, W. A.; Janda, K. D. J Org Chem 2000, 65, 8527; (e) Behrendt, J. M.; Bala, K.; Golding, P.; Hailes, H. C. Tetrahedron Lett 2005, 46, 643.