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RESEARCH ARTICLE

Acceleration of Multicomponent Reactions in Aqueous Medium: Multicomponent Synthesis of a 4*H*-pyran Library

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Abstract: A combinatorial library of 2-amino-4*H*-pyran derivatives has been developed by a three-component reaction between aldehyde, malononitrile and *β*-dicarbonyl compounds (ethyl acetoacetate or acetylacetone) in the presence of ammonium acetate in aqueous medium. This protocol couples the benefits of multi-component reaction (MCR) with those of water as solvent for organic transformations, thus facilitating efficient chemical production in an environmentally benign way.

Keywords*:* 2-Amino-4H-pyran, One-pot reaction, Multi-component reaction, Aqueous medium.

Introduction

Green chemistry emphasizes the development of environmentally benign chemical processes and technologies[1]. The use of water as a solvent for organic transformations offers several "green chemistry" benefits[2]. In many reactions, such as the Diels-Alder cycloaddition[3], significant rate enhancements are observed in water compared to organic solvents. This acceleration has been attributed to many factors, including the hydrophobic effect[4], enhanced hydrogen bonding in the transition state[5] and the high cohesive energy density of water (550.2 cal.mL^{-1} at 25 ˚C)[6]. The Diels-Alder reaction is also known for its negative activation volume, owing to a transition state that is more compact than reactants. Reactions with negative activation volumes are accelerated at high pressure and with nonpolar reactants, in water[7].

The multicomponent reactions important in combinatorial chemistry[8] are predicted to exhibit negative activation volumes owing to the condensation of several molecules into a single reactive intermediate and product[9]. Thus, not only does the use of water as solvent permit multicomponent reactions to be conducted rapidly, the products are often insoluble, facilitating their ready isolation. This method permits rapid syntheses of compound libraries. 4*H*-Pyans and their derivatives are an important class of bioactive molecules in the field of drug and pharmaceuticals[10]. These compounds are used as anti-coagulants, anticancer agents, spasmolytics, anti-anaphylactics[11,12]. 2-amino-4H-pyran derivatives often used in cosmetic and pigments and utilized as potentially biodegradable agrochemicals[13-15]. Moreover, these compounds can be used in various applications as cognitive enhancer for the treatment of neuro degenerative diseases, including Alzheimer's disease, as well as for

the treatment of schizophrenia and myoclonus[16,17]. 4*H*-Pyran derivatives are also potential calcium channel antagonists [18] which are structurally similar to biologically active 1,4-dihydropyridines (1,4-DHPs).

Generally, 2-amino-4-aryl-3-cyano-4*H*-pyrans were synthesized by the cyclization of arylidenemalononitriles and active methylene compounds in the presence of organic bases such as piperidine[19], pyridine[20], triethylamine[21,22]. Most of these methods involve use of volatile solvents and require longer reaction time (~ 12 h) and difficult to recover catalyst. Moreover, the cyclization arylidenemalononitriles and ethyl acetoacetate in the presence of triethylbenzylammonium chloride, as phase-transfer catalysts, in an aqueous medium has been reported[23]. Recently, one-pot synthesis of these compounds has been reported using Mg/La mixed oxide[24], MgO[25,26] and tetramethylguanidine[27] as basic catalyst.

Herein, we report three-component reaction of aromatic aldehydes, ethyl acetoacetate/ or acetylacetone, and malononitrile in the presence of ammonium acetate for a combinatorial synthesis of 2-amino-4*H*-pyran frame-works in aqueous medium (Scheme 1).

Experimental

The ^{1}H- and ^{13}C-NMR spectra were taken on a Bruker SP-400 AVANCE, a Bruker SP-300 AVANCE or a Bruker SP-250 AVANCE spectrometers. The IR spectra were recorded on a Bruker PS-15 spectrometer. Mass spectra were recorded on a Varian MAT 311A instrument using an ionizing current of 70 eV. The elemental analyses were performed on a Carlo-Erba 1104 CHN analyzer. The melting points were measured on an Electrothermal 9100 apparatus in open capillaries without correction. All the commercial reagents were used without prior purification.

General procedure

To a stirred mixture of aldehyde (1 mmol), malononitrile (1 mmol), ammonium acetate (1.3 mmol) in water-ethanol (1:1, 3 mL) at 55 ^{o}C was added ethyl acetoacetate (1 mmol)/ or acetylacetone. The mixture was stirred at this temperature under an open atmosphere till the completion of reaction as indicated by TLC, after which it was cooled and the precipitated soild was filtered, washed with water and recrystallized from ethanol.

*Ethyl 2-amino-3-cyano-6-methyl-4-phenyl-4H-pyran-5-carboxylate (**2a**)*

White powder, mp 190-191.5 °C; IR spectrum (KBr) ν, cm^{-1}: 3402 (s), 3328 (s), 3223 (m), 2966 (w), 2189 (s), 1693(s), 1259 (s), 1060 (s). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.10 (3H, t, *J*=7.20, CH_3 ester), 2.38 (3H,s, CH_3-2), 4.05 (2H, m, CH_2 ester), 4.45 (1H, s, C(4)-H), 4.50 (2H, br, s, NH_2), 7.17-7.35 (5H, m, Ar-H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.86 (CH_3 ester), 18.37 (CH_3-2), 38.75 (C-4), 60.64 (CH_2 ester), 62.58 (C-3), 108.00 (C-5), 118.80 (CN), 127.17 (C-4′), 127.50 (C-3′,5′), 128.56 (C-2′,6′), 143.72 (C-1′), 156.76, 157.39 (C-2, 6), 165.83 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 284 [M^{+}] (19.70), 255 (23.03), 211 (10.32), 207 (100), 179 (18.23), 161 (11.16). Found, %: C 67.47; H 5.77; N 9.90. $C_{16}H_{16}N_2O_3$. Calculated, %: C 67.59; H 5.67; N 9.85.

*Ethyl 2-amino-3-cyano-6-methyl-4-(3-hydroxyphenyl)-4H-pyran-5-carboxylate (**2b**)*

Pale yellow solid; mp 191-192 ^{o}C; IR spectrum (KBr) ν, cm^{-1}: 3402 (s), 3328 (s), 3223 (m), 2966 (w), 2189 (s), 1693 (s), 1259 (s) and 1060 (s). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.12 (3H, t, *J* =6.90, CH_3 ester), 2.38 (3 H, s, CH_3-6), 4.06 (2H, m, CH_2 ester), 4.41 (1H, s, OH), 4.44 (2H, br s, NH_2), 4.80 (1H, s, C(4)-H), 6.67–7.19 (4H, m, Ar-H).

*Ethyl 2-amino-3-cyano-6-methyl-4-(2-nitrophenyl)-4H-pyran-5-carboxylate (**2c**)*

Yellow crystals; mp 177.5-178.5 °C; IR spectrum (KBr) ν, cm^{-1}: 3453 (s), 3294 (s), 3215 (s), 3185(s), 2984 (w), 2208 (s), 1719(s), 1684 (s), 1601 (s), 1530 (s), 1381 (s), 1225 (s), 1062 (s), 786 (s), 726 (s). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.99 (3H, t, *J*=7.20, CH_3 ester), 2.41 (3H, s, CH_3-6), 3.96 (2H, m, CH_2 ester), 4.67(br, s, NH_2), 5.26 (1H, s, C(4)-H), 7.32-7.40 (2H, m, Ar-H4´,H6´), 7.58 (1H, dt, J_1=7.50, J_2=1.20, Ar-H5´), 7.82 (1H, dd, J_1=7.70, J_2=1.20, Ar-H3´). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.66 (CH_3 ester), 18.45 (CH_3-6), 32.97 (C-4), 60.95 (CH_2 ester), 63.50 (C-3), 107.30 (C-5), 118.21 (CN), 124.06 (C-3´), 127.91 (C-4´), 130.61 (C-6´), 133.23 (C-5´), 139.08 (C-1´), 149.09 (C-2´), 158.05, 158.24 (C-2, 6), 165.04 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 329 [M^+] (0.52), 312 (100), 284 (6.52), 267 (57.27), 253 (9.62), 238 (24.89), 195 (34.44), 179 (9.02), 140 (10.22). Found, %: C 57.90; H 4.54; N 12.71. $C_{16}H_{15}N_3O_5$. Calculated, %: C 58.36; H 4.59; N 12.76.

*Ethyl 2-amino-3-cyano-6-methyl-4-(3-nitrophenyl)-4H-pyran-5-carboxylate (**2d**)*

Yellow crystals, mp.187-188 °C; IR spectrum (KBr) ν, cm^{-1}: 3402 (s), 3328 (s), 3221 (m), 2987 (w), 2190 (s), 1672(s), 1531 (s), 1344 (s), 1063 (s). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.12 (3H, t, *J*=7.20, CH_3 ester), 2.41 (3H, s, CH_3-6), 4.05 (2H, m, CH_2 ester), 4.58 (1H, s, C(4)-H), 4.69(br, s, NH_2), 7.49 (1H, t, *J*=8.00, Ar-H5´), 7.58 (1H, d, *J*=8.00, Ar-H6´), 8,06 (1H, t, *J*=1.60, Ar-H2´), 8,11 (1H, d, *J*=8.00, Ar-H4´). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 12.90 (CH_3 ester), 17.64 (CH_3-6), 37.75 (C-4), 59.95 (CH_2 ester), 63.50 (C-3), 105.93 (C-5), 117.33 (CN), 121.39 (C-4´), 121.55 (C-2´), 128.51 (C-5´), 133.01 (C-6´), 145.10 (C-1´), 147.47 (C-3´), 159.77, 156.95 (C-2, 6), 164.26 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 329 [M^+] (6.86), 312 (65.94), 300 (11.52), 282 (7.38), 256 (5.30), 207 (100), 179 (44.23), 161 (24.45). Found, %: C 58.44; H 4.55; N 12.98. $C_{16}H_{15}N_3O_5$. Calculated, %: C 58.36; H 4.59; N 12.76.

*Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**2e**)*

Yellow crystals; mp 175-176 °C; IR spectrum (KBr) ν, cm^{-1}: 3404 (s), 3333 (s), 3204 (s), 2983 (w), 2200 (s), 1690(s), 1650 (s), 1518 (s), 1345 (s), 1270 (s), 1060 (s). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.11 (3H, t, *J*=7.20, CH_3 ester), 2.42 (3H, s, CH_3-6), 4.05 (2H, q, *J*=7.20, CH_2 ester), 4.57 (1H, s, C(4)-H), 4.67(br, s, NH_2), 7.39 (2H, d, *J*=7.70, Ar-H2´,6´), 8.18 (1H, d, *J*=7.70, Ar-H3´,5´). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.92 (CH_3 ester), 18.61 (CH_3-6), 38.82 (C-4), 60.86 (C-3), 60.97 (CH_2 ester), 106.79 (C-5), 118.28 (CN), 123.99 (C-2´,6´), 128.42 (C-3´,5´), 147.09 (C-1´), 151.09 (C-4´), 157.73, 158.05 (C-2, 6), 165.26 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 329 [M^+] (31.19), 312 (2.94), 300 (57.42), 284 (7.81), 256 (19.23), 246 (12.34), 207 (100), 179 (22.40), 161 (13.65). Found, %: C 58.67; H 4.47; N 12.73. $C_{16}H_{15}N_3O_5$. Calculated, %: C 58.36; H 4.59; N 12.76.

*Ethyl 2-amino-3-cyano-6-methyl-4-(2-methoxyphenyl)-4H-pyran-5-carboxylate (**2f**)*

White crystals; mp 196-197 °C; IR spectrum (KBr) ν, cm^{-1}: 3403 (s), 3326 (s), 3220 (m), 2967 (w), 2933 (w), 2187 (s), 1693(s), 1606 (m), 1256 (s), 1063 (s), 713 (s). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.06 (3H, t, *J*=7.20, CH_3 ester), 2.38 (3H, s, CH_3-6), 3.84 (3H, s, OCH_3), 4.00 (2H, m, CH_2 ester), 4.41 (2H, br, s, NH_2), 4.88 (1H, s, C(4)-H), 6.82-6.92 (2H, m, Ar-H5´, 3´), 7.06 (1H, dd, J_1=7.50, J_2=1.50, Ar-H6´), 7.19 (1H,

dt, J_1=7.50, J_2=1.50, Ar-H4´). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.77 (CH_3 ester), 18.31 (CH_3-6), 32.61 (C-4), 55.58 (OCH_3), 60.42 (CH_2 ester), 61.81 (C-3), 107.06 (C-5), 111.05 (C-3´), 119.10 (CN), 120.65 (C-5´), 128.24 (C-4´), 128.68 (C-6´), 131.79 (C-1´) 157.07 (C-2), 157.45 (C-2´), 157.94 (C-6), 166.08 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 314 [M^+] (57.99), 285 (100), 268 (59.86), 237 (43.95), 225 (42.75), 207 (65.98), 179 (23.36), 161 (20.33). Found, %: C 65.00; H 5.85; N 9.10. $C_{17}H_{18}N_2O_4$. Calculated, %: C 64.96; H 5.77; N 8.91.

Ethyl 2-amino-3-cyano-6-methyl-4-(3-methoxyphenyl)-4H-pyran-5-carboxylate ***(2g)***

White crystals; mp 147-148 °C; IR spectrum (KBr) ν, cm^{-1}: 3391 (s), 3327 (s), 3265 (m), 3224 (m), 2932 (w), 2192 (s), 1690 (s), 1648 (s), 1601 (s), 1263 (s), 1061 (s), 786 (m). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.12 (3H, t, *J* =6.90, CH_3 ester), 2.37 (3H, s, CH_3-6), 3.79 (3H, s, OCH_3), 4.04 (2H, m, CH_2 ester), 4.42 (1H, s, C(4)-H), 4.50 (2H, br s, NH_2), 6.74 (1H, s, Ar-H2'), 6.78 (1H, t, *J* =7.8, Ar-H5'), 7.21 (1H, d, *J* =7.8, Ar-H4'), 7.25 (1H, d, *J* =7.8, Ar-6'). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 13.91 (CH_3 ester), 18.38 (CH_3-6), 38.73 (C-4), 55.18 (OCH_3), 60.65 (C-3), 62.21 (CH_2 ester), 107.86 (C-5), 112.19 (C-3'), 113.58 (C-2'), 118.87 (CN), 119.92 (C-6'), 129.54 (C-5'), 145.42 (C-1'), 156.82 (C-2), 157.54 (C-3'), 159.75 (C-6), 165.83 (CO).

Ethyl 2-amino-3-cyano-6-methyl-4-(2-chlorophenyl)-4H-pyran-5-carboxylate ***(2h)***

White crystals; mp. 191-192 °C; IR spectrum (KBr) ν, cm^{-1}: 3428 (s), 3331 (s), 3195 (w), 2194 (s), 1685 (s), 1604 (m), 1261 (s), 1062 (s), 743 (s) cm^{-1}; ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.04 (t, *J*=7.20 Hz, 3H, CH_3 ester), 2.40 (3H, s, CH_3-6), 3.99 (2H, m, CH_2 ester), 4.48 (br, s, NH_2), 5.05 (1H, s, C(4)-H), 7.12-7.23 (3H, m, Ar-H), 7.33 (1H, d, *J*=8.00, Ar-H3´). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 12.71 (CH_3 ester), 17.30 (CH_3-6), 34.35 (C-4), 59.67 (CH_2 ester), 60.27 (C-3), 105.88 (C-5), 117.45 (CN), 126.26 (C-5´), 127.32 (C-4´), 128.76 (C-3´, 6´), 132.08 (C-2´), 140.06 (C-1´), 156.52, 156.80 (C-2, 6), 164.56 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 320 [M^+] (3.62), 318 [M^+] (10.59), 291 (8.54), 289 (25.16), 283 (37.11), 207 (100), 179 (31.15), 161 (17.59). Found, %: C 60.10; H 4.78; N 8.56. $C_{16}H_{15}ClN_2O_3$. Calculated, %: C 60.29; H 4.74; N 8.79.

Ethyl 2-amino-3-cyano-6-methyl-4-(3-chlorophenyl)-4H-pyran-5-carboxylate ***(2i)***

White crystals; mp. 180-180.5 °C; IR spectrum (KBr) ν, cm^{-1}: 3400 (s), 3325 (s), 3220 (s), 2984 (w), 2192 (s), 1694 (s), 1647 (s), 1603 (s), 1265 (s), 1060 (s), 778 (s). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.12 (3H, t, *J*=6.90, CH_3 ester), 2.38 (3H, s, CH_3-6), 4.04 (2H, m, CH_2 ester), 4.42 (1H, s, C(4)-H), 4.59 (br, s, NH_2), 7.01-7.30 (4H, m, Ar-H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.88 (CH_3 ester), 18.48 (CH_3-6), 38.62 (C-4), 60.78 (CH_2 ester), 61.62 (C-3), 107.43 (C-5), 118.62 (CN), 125.92 (C-4´), 127.44 (C-6´), 127.69 (C-2´), 129.81 (C-5´),134.39 (C-3´), 145.88 (C-1´), 157.29, 157.64 (C-2, 6), 164.56 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 320 [M^+] (5.08), 318 [M^+] (15.27), 291 (7.44), 289 (20.39), 273 (7.57), 245 (12.69), 207 (100), 179 (32.86), 161 (19.00). Found, %: 60.13; H 4.70; N 8.56. $C_{16}H_{15}ClN_2O_3$. Calculated, %: C 60.29; H 4.74; N 8.79.

Ethyl 2-amino-3-cyano-6-methyl-4-(2-bromophenyl)-4H-pyran-5-carboxylate ***(2j)***

White crystals; mp. 183-184 °C; IR spectrum (KBr) ν, cm^{-1}: 3431 (s), 3336 (s), 3195 (w), 2190 (s), 1685 (s), 1641 (m), 1602 (m), 1260 (s), 1061 (s), 742 (s). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.04 (3H, t, *J*=7.20, CH_3 ester), 2.39 (3H, s, CH_3-6), 3.99 (2H, m, CH_2 ester), 4.51 (br, s, NH_2), 5.06 (1H, s, C(4)-H), 7.06 (1H, dt, J_1=7.60, J_2=1.60, Ar-H4´), 7.14 (1H, dd, J_1=7.60, J_2=1.60, Ar-H6´), 7.25 (1H, dt, J_1=7.60, J_2=1.60, Ar-H5´),

7.52 (1H, dd, J_1=7.60, J_2=1.60, Ar-H3´). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 12.78 (CH_3 ester), 17.28 (CH_3-6), 36.60 (C-4), 59.67 (CH_2 ester), 60.27 (C-3), 106.14 (C-5), 117.38 (CN), 122.35 (C-2´), 126.96 (C-5´), 127.55 (C-4´), 128.73 (C-6´), 132.01 (C-3´), 141.89 (C-1´), 156.45, 156.70 (C-2, 6), 164.56 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 364 [M^+] (4.55), 362 [M^+] (4.55), 335 (11.57), 333 (11.57), 291 (7.43), 289 (7.37), 283 (41.14), 207 (100), 179 (30.17), 161 (15.93). Found, %: C 52.61; H 4.13; N 7.60. $C_{16}H_{15}BrN_2O_3$. Calculated, %: C 52.91; H 4.19; N 7.71.

*Ethyl 2-amino-3-cyano-6-methyl-4-(4-bromophenyl)-4H-pyran-5-carboxylate (**2k**)*

White crystals; mp. 180-181 °C; IR spectrum (KBr) ν, cm^{-1}: 3409 (s), 3329 (s), 3224 (w), 2194 (s), 1690 (s), 1641 (m), 1608 (m), 1264 (s), 1068 (s), 835 (m), 756 (w). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.11 (3H, t, *J*=6.90, CH_3 ester), 2.35 (3H, s, CH_3-6), 4.03 (2H, q, *J*=6.90, CH_2 ester), 4.40 (1H, s, C(4)-H), 4.66 (br, s, NH_2), 7.08 (2H, d, *J*=8.40, Ar-H2´,6´), 7.42 (2H, d, *J*=8.40, Ar-H3´,5´). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.92 (CH_3 ester), 18.47 (CH_3-6), 38.39 (C-4), 60.78 (CH_2 ester), 61.37 (C-3), 107.47 (C-5), 118.79 (CN), 121.03 (C-4´), 129.29 (C-2´, 6´), 131.66 (C-3´,5´), 142.99 (C-1´), 157.13, 157.68 (C-2, 6), 165.66 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 364 [M^+] (17.28), 362 [M^+] (17.19), 335 (24.19), 333 (23.43), 291 (13.62), 289 (13.07), 207 (100), 179 (20.26), 161 (11.70). Found, %: C 52.65; H 4.10; N 7.36. $C_{16}H_{15}BrN_2O_3$. Calculated, %: C 52.91; H 4.19; N 7.71.

*Ethyl 2-amino-3-cyano-6-methyl-4-(2-methylphenyl)-4H-pyran-5-carboxylate (**2l**)*

White crystals; mp. 140-141 °C; IR spectrum (KBr) ν, cm^{-1}: 3426 (s), 3332 (s), 3202 (m), 2194 (s), 1690 (s), 1647 (m), 1608 (m), 1370 (m), 1259 (s), 1061 (s), 742 (s). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.03 (3H, t, *J*=7.20, CH_3 ester), 2.38 (3H, s, CH_3-6), 2.49 (3H, s, CH_3), 3.98 (2H, m, CH_2 ester), 4.51 (br, s, NH_2), 4.77 (1H, s, C(4)-H), 7.10 (4H, m, Ar-H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.91 (CH_3 ester), 18.34 (CH_3-6), 19.27 (CH_3), 34.15 (C-4), 60.60 (CH_2 ester), 61.71 (C-3), 108.04 (C-5), 119.12 (CN), 126.59, 126.85 (C-4´, 5´), 127.87, 130.37 (C-3´, 6´), 135.21 (C-1´), 142.47 (C-2´), 157.02, 157.42 (C-2, 6), 165.91 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 298 [M^+] (18.40), 269 (13.89), 253 (6,69), 225 (8.35), 207 (100), 179 (28.92), 161 (15.53). Found, %: C 68.65; H 5.98; N 9.20. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.44; H 6.08; N 9.39.

*Ethyl 2-amino-3-cyano-6-methyl-4-(3-methylphenyl)-4H-pyran-5-carboxylate (**2m**)*

White crystals; mp 176-177 °C; IR spectrum (KBr) ν, cm^{-1}: 3401 (s), 3330 (m), 3222 (m), 2981 (w), 2192 (s), 1697 (s), 1675 (s), 1647 (m), 1604 (m), 1372 (m), 1266 (s), 1058 (s), 721 (m). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.11 (3H, t, *J*=6.90, CH_3 ester), 2.33 (3H, s, CH_3-6), 2.38 (3H, s, CH_3), 4.05 (2H, m, CH_2 ester), 4.41 (1H, s, C(4)-H), 4.45 (br, s, NH_2), 6.92-7.25 (4H, m, Ar-H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.86 (CH_3 ester), 18.37 (CH_3-6), 21.45 (CH_3), 38.68 (C-4), 60.61 (CH_2 ester), 62.52 (C-3), 108.08 (C-5), 118.91 (CN), 124.62 (C-4´), 127.96, 128.20, 128.40 (C-2´, 5´, 6´), 138.07 (C-3´), 143.64 (C-1´), 156.61, 157.45 (C-2, 6), 165.91 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 298 [M^+] (20.38), 269 (12.79), 207 (100), 179 (35.92), 161 (18.22). Found, %: C 68.52; H 6.12; N 9.25. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.44; H 6.08; N 9.39.

*Ethyl 2-amino-3-cyano-6-methyl-4-(4-methylphenyl)-4H-pyran-5-carboxylate (**2n**).*

White crystals; mp 175-176 °C; IR spectrum (KBr) ν, cm^{-1}: 3409 (s), 3332 (s), 3229 (w), 2197 (s), 1695 (s), 1611 (m), 1581 (m), 1263 (s), 1064 (s), 857 (w), 756 (w). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.27 (3H, t, *J* =6.90, CH_3 ester), 2.31 (3H, s, CH_3-6), 2.36 (3H, s, CH_3),.4.03 (2H, q, *J* =6.90, CH_2 ester), 4.41 (1H, s, C(4)-H), 4.54 (br s,

2H, NH_2), 7.09 (4H, s, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 13.90 (CH_3 ester), 14.21 (CH_3), 18.37 (CH_3-6), 38.39 (C-4), 60.20 (C-3), 60.64 (CH_2 ester), 108.12 (C-5), 127.37 (C-3', 5'), 128.40 (CN), 129.24 (C-2', 6'), 129.90 (C-4'), 136.71 (C-1'), 156.55, 157.56 (C-2, 6), 165.96 (CO).

*Ethyl 2-amino-3-cyano-6-methyl-4-(2-furyl)-4H-pyran-5-carboxylate (**2o**)*

Orange crystals; mp 203-204 °C; IR spectrum (KBr) ν, cm^{-1}: 3393 (m), 3370 (m), 3202 (m), 2963 (m), 2193 (s), 1693(s), 1685 (s), 1261 (s), 1065 (s), 802 (s). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.23 (3H, t, *J*=7.20, CH_3 ester), 2.37 (s, 3H, CH_3-6), 4.16 (2H, m, CH_2 ester), 4.53 (2H, br, s, NH_2), 4.64 (1H, s, C(4)-H), 6.102 (1H, d, *J*=3.30, Ar-H5´), 6.28 (1H, m, Ar-H4´), 7.31 (1H,s, Ar-H3´). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 14.00 (CH_3 ester), 18.43 (CH_3-6), 32.37 (C-4), 59.53 (C-3), 60.78 (CH_2 ester), 105.71 (C-5), 105.93 (C-5´), 110.33 (C-4´), 118.62 (CN), 141.93 (C-3´), 155.13 (C-1´), 157.78 , 158.54 (C-2, 6), 165.63 (CO). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 274 [M^+] (34.20), 246 (74.15), 229 (28.69), 213 (24.79), 201 (100), 185 (20.53), 172 (16.82), 158 (81.04). Found, %: C 61.25; H 5.20; N 10.31. $C_{14}H_{14}N_2O_4$. Calculated, %: C 61.31; H 5.14; N 10.21.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-phenyl-4H-pyran (**3a**)*

White crystals; mp 154.5-155.5 °C; IR spectrum (KBr) ν, cm^{-1}: 3380 (s), 3201 (m), 2199 (s), 1693(s), 1667 (s), 1594 (s), 1217 (s), 700 (s). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.10 (3H, s, CH_3), 2.20 (3H, s, CH_3), 4.43 (1H, s, C(4)-H), 6.81 (2H, s, NH_2), 7.17-7.35 (5H, m, Ar-H). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 18.87 (CH_3-6), 30.21 (CH_3 acetyl), 38.94 (C-4), 58.25 (C-3), 115.44 (C-5), 120.22 (CN), 127.39 (C-4´), 127.58 (C-3´,5´), 129.18 (C-2´,6´), 145.00 (C-1´), 155.21, 158.69 (C-2,6), 198.81 (CO).

*5-Acetyl-2--amino-3-cyano-6-methyl-4-(3-hydroxyphenyl)-4H-pyran (**3b**)*

Pale yellow powder; mp 167-168 °C; IR spectrum (KBr) ν, cm^{-1}: 3385 (m), 3342 (s), 3297 (m), 2195 (s), 1694 (s), 1659 (s), 1588 (s), 1221 (m). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.04 (3H, s, CH_3), 2.20 (3H, s, CH_3), 4.34 (1H, s, C(4)-H), 6.79 (2H, br.s, NH_2), 6.56-6.60 and 7.06-7.12 (4H, m, ArH), 9.41(1H, s, OH). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 18.81 (CH_3-6), 30.13 (CH_3 acetyl), 38.83 (C-4), 58.32 (C-3), 114.38 (C-5), 114.52 (C-4'), 115.54 (C-2'), 118.23 (C-6'), 120.30 (CN), 13.15 (C-5'), 146.41 (C-1'), 155.00 (C-2), 158.08 (C-3'), 158.71 (C-6), 198.93 (CO). Found, %: C 66.42; H 5.21; N 10.30. $C_{15}H_{14}N_2O_3$. Calculated, %: C 66.65; H 5.22; N 10.36.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(2-nitrophenyl)-4H-pyran (**3c**)*

Yellow crystals, mp 183-184(Dec.) °C; IR spectrum (KBr) ν, cm^{-1}: 3453 (s), 3328 (m), 2200 (s), 1681 (s), 1652 (s), 1526 (s), 1383 (s). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.08 (3H, s, CH_3), 2.23 (3H, s, CH_3), 4.60 (1H, s, C(4)-H), 6.98 (br.s, NH_2), 7.40-8.10 (4H, m, Ar-H). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 19.20 (CH_3-6), 30.52 (CH_3 acetyl), 38.97 (C-4), 57.50 (C-3), 115.00 (C-5), 119.21 (CN), 124.06 (C-3´), 128.90 (C-4´), 131.61 (C-6´), 133.03 (C-5´), 139.08 (C-1´), 149.09 (C-2´), 157.25, 158.24 (C-2, 6), 198.04 (CO). Found, %: C 60.23; H 4.47; N 13.92. $C_{15}H_{13}N_3O_4$. Calculated, %: C 60.19; H 4.37; N 14.04.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(3-nitrophenyl)-4H-pyran (**3d**)*

Pale orange crystals; mp 214-215 °C; IR spectrum (KBr) ν, cm^{-1}: 3392 (s), 3323 (m), 3210 (m), 2189 (s), 1674 (s), 1640 (s), 1528 (s), 1380 (s). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.08 (3H, s, CH_3), 2.26 (3H, s, CH_3), 4.66 (1H, s, C(4)-H), 6.99 (2H, s,

NH_2), 7.62-8.08 (4H, m, Ar-H). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 19.19 (CH_3-6), 30.57 (CH_3 acetyl), 38.90 (C-4), 57.33 (C-3), 115.02 (C-5), 119.90 (CN), 121.96 (C-4′), 122.49 (C-2′), 130.82 (C-5′), 134.40 (C-6′), 147.38 (C-1′), 148.44 (C-3′), 156.57, 159.04 (C-2, 6), 198.29 (CO). Found, %: C 60.20; H 4.45; N 14.10. $C_{15}H_{13}N_3O_4$. Calculated, %: C 60.19; H 4.37; N 14.04.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(4-nitrophenyl)-4H-pyran (**3e**)*

Yellow crystals; mp 180-181 °C; IR spectrum (KBr) ν, cm^{-1}: 3412 (s), 3340 (s), 2192 (s), 1701 (m), 1681(s), 1664 (s), 1508 (m), 1345 (s). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.02 (3H, s, CH_3), 2.20 (3H, s, CH_3), 4.62 (1H, s, C(4)-H), 7.01(2H, br.s, NH_2), 7.44 (2H, d, *J*=8.00, Ar-H2′,6′), 8.18 (2H, d, *J*=8.00, Ar-H3′,5′). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 19.23 (CH_3-6), 30.56 (CH_3 acetyl), 38.92 (C-4), 57.03 (C-3), 114.89 (C-5), 119.85 (CN), 124.50 (C-2′,6′), 128.84 (C-3′,5′), 146.90 (C-1′), 152.54 (C-4′), 156.69, 159.02 (C-2, 6), 198.19 (CO). Found, %: C 60.13; H 4.45; N 13.98. $C_{15}H_{13}N_3O_4$. Calculated, %: C 60.19; H 4.37; N 14.04.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(3-methoxyphenyl)-4H-pyran (**3f**)*

White crystals; mp 180-181 °C; IR spectrum (KBr) ν, cm^{-1}: 3355 (s), 3187 (s), 2193 (s), 1677 (s), 1634 (s), 1205 (s). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.04 (3H, s, CH_3), 2.21 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.42 (1H, s, C(4)-H), 6.69-6.78 (3H, m, Ar-H2',4',6'), 6.82 (2H, br.s, NH_2), 7.24 (1H, t, *J* =7.60, Ar-H5'). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 18.84 (CH_3-6), 30.21 (CH_3 acetyl), 38.84 (C-4), 55.40 (C-3), 58.13 (OCH_3), 112.18 (C-5), 113.78 (C-4'), 115.28 (C-2'), 119.73 (C-6'), 120.25 (CN), 130.38 (C-5'), 146.58 (C-1'), 155.28 (C-2), 158.74 (C-3'), 159.89 (C-6), 198.88 (CO). Found, %: C 67.57; H 5.66; N 9.97. $C_{16}H_{16}N_2O_3$. Calculated, %: C 67.59; H 5.67; N 9.85.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(3-methylphenyl)-4H-pyran (**3g**)*

White crystals; mp 191.5-192 °C; IR spectrum (KBr) ν, cm^{-1}: 3372 (br., s), 3194 (m), 2190 (s), 1676 (s), 1637 (s). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.04 (3H, s, CH_3 acetyl), 2.23 (3H, s, CH_3-2), 2.26 (3H, s, CH_3), 4.68 (1H, s, C(4)-H), 6.81 (2H, br.s, NH_2), 7.00-7.48 (4H, m, Ar-H). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 18.85 (CH_3-6), 21.52 (CH_3), 30.21 (CH_3 acetyl), 38.90 (C-4), 58.37 (C-3), 115.46 (C-5), 120.26 (CN), 124.80 (C-4′), 128.06, 128.14, 129.06 (C-2′, 5′, 6′), 138.33 (C-3′), 144.96 (C-1′), 155.10, 158.69 (C-2, 6), 198.87 (CO). Found, %: C 71.42; H 5.97; N 10.37. $C_{16}H_{12}N_2O_2$. Calculated, %: C 71.62; H 6.01; N 10.44.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(2-chlorophenyl)-4H-pyran (**3h**)*

White crystals; mp 143.5-144 °C; IR spectrum (KBr) ν, cm^{-1}: 3386 (m), 3331 (m), 3195 (m), 2195(m), 1686 (s), 1654 (s), 1221 (m). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.02 (3H, s, CH_3), 2.22 (3H, s, CH_3), 4.95 (1H, s, C(4)-H), 6.69 (2H, br.s, NH_2), 7.15-7.37 (4H, m, Ar-H). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 18.99 (CH_3-6), 29.96 (CH_3 acetyl), 36.05 (C-4), 56.77 (C-3), 114.68 (C-5), 119.68 (CN), 128.48 (C-5′), 129.15 (C-4′), 130.04 (C-3′), 130.45 (C-6′), 132.14 (C-2′), 141.94 (C-1′), 156.52, 156.80 (C-2, 6), 198.25 (CO). Found, %: C 62.01; H 4.47; N 9.38. $C_{15}H_{13}ClN_2O_2$. Calculated, %: C 62.39; H 4.53; N 9.70.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(3-chlorophenyl)-4H-pyran (**3i**)*

White crystals; mp. 194-195 °C; IR spectrum (KBr) ν, cm^{-1}: 3356 (m), 3192 (m), 2193 (s), 1677 (s), 1636 (s). ^1H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.81 (3H, s,

CH_3), 2.23 (3H,s, CH_3), 4.48 (1H,s, C(4)-H), 6.91 (2H, br.s, NH_2), 7.10-7.63 (4H, m, Ar-H). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 19.03 (CH_3-6), 30.40 (CH_3 acetyl), 38.81 (C-4), 57.64 (C-3), 115.05 (C-5), 120.04 (CN), 126.36 (C-4´), 127.31 (C-6´), 127.47 (C-2´), 131.15 (C-5´), 133.76 (C-3´), 147.56 (C-1´), 155.94, 158.87 (C-2, 6), 198.56 (CO). Found, %: C 62.26; H 4.47; N 9.46. $C_{15}H_{13}ClN_2O_2$. Calculated, %: C 62.39; H 4.53; N 9.70.

*5-Acetyl-2-amino-3-cyano-6-methyl-4-(2-furyl)-4H-pyran (**3j**)*

White crystals; mp 180-181 °C; IR spectrum (KBr) ν, cm^{-1}: 3400 (s), 3320 (m), 3100 (m), 2188 (s), 1673(s), 1653 (s), 740 (m). ^{1}H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.17 (6H, s, 2×CH_3), 4.32 (1H, s, C(4)-H), 6.12 (1H, d, *J*=2.60, Ar-H5´), 6.34 (1H, s, Ar-H4´), 6.92 (2H, s, NH_2), 7.52 (1H, s, Ar-H3´). ^{13}C NMR spectrum (62.5 MHz, DMSO-d_6), δ, ppm: 19.00 (CH_3-6), 29.93 (CH_3 acetyl), 32.98 (C-4), 54.92 (C-3), 106.08 (C-5), 110.94 (C-5´), 113.51 (C-4´), 120.12 (CN), 142.91 (C-3´), 156.19 (C-1´), 156.39, 159.95 (C-2, 6), 198.32 (CO). Found, %: C 63.62; H 4.58; N 10.76. $C_{13}H_{12}N_2O_3$. Calculated, %: C 63.92; H 4.95; N 11.47.

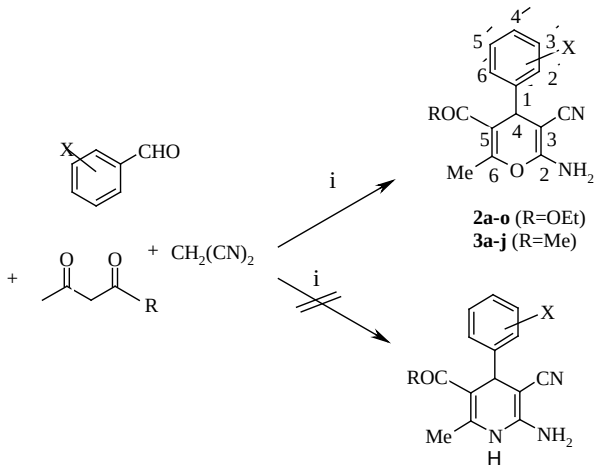
Results and Discussion

In order to achieve optimum conditions, we initially investigated the three-component reaction of benzaldehyde **1a** (1 equiv.), malononitrile (1 equiv.), and ethyl acetoacetate (1 equiv.) in the presence of ammonium acetate (1.3 equiv.) in different conditions as shown in Table 1. The reaction did not proceed to completion when water was employed as solvent. The reaction was found to proceed sluggishly both at ambient temperature and at reflux conditions and the desired product **2a** was obtained in only 42% yield after 2.5 h under reflux conditions (Table 1, entry 2). When using ethanol as solvent, the corresponding product was also obtained in low yields (Table 1, entries 3-4). Therefore, mixtures of water-ethanol were examined (Table 1, entries 5-7). Acceleration in reaction rate was observed. The best result was obtained when the reaction was carried out in water-ethanol (1:1 v/v) at 55 ^{o}C (Table 1, entry 6). Note that in using 2:1 ratio of water-ethanol as the solvent at 55 ^{o}C, the solvent must be twice that of used for the previous experiment (entry 7 *vs.* 6). The optimized reaction conditions were then applied to a range of aldehyde substrates (Table 2, entries 1-15). Both electron-poor and electron-rich aldehydes were well tolerated. Notably, despite using so much ammonium acetate, no 1,4-dihydropyridine product was detected (Scheme 1).

Table 1. Optimization Studies: Effect of Temperature and Solvent on the Reaction[a]

Entry	Solvent	Temp, $^{\circ}$C	Time, min	Yield of **2a**[b], %
1	H_2O	25	120	20
2	H_2O	97	150	42
3	EtOH	25	120	23
4	EtOH	55	45	57
5	EtOH/H_2O(1:1)	25	120	76
6	EtOH/H_2O (1:1)	55	5	87
7	EtOH/H_2O (1:2)[c]	55	5	87

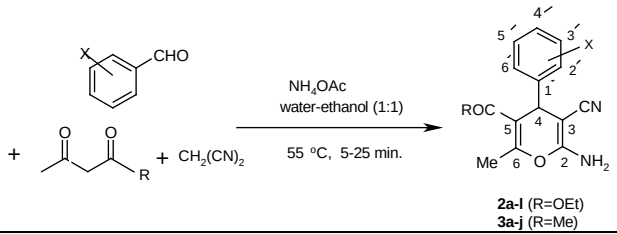
*[a]All reactions performed with benzaldehyde **1a** (1 equiv.), malononitrile (1 equiv.), ethyl acetoacetate (1 equiv.), and ammonium acetate (1.3 equiv.). [b]Isolated yields after recrystallization. [c]The amount of solvent must be twice that of used for entry 6*

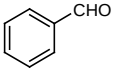
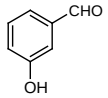
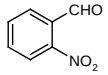


Scheme 1. Multicomponent synthesis of a 4H-pyran library. i) NH4OAc, water-ethanol (1:1), 55 ^{o}C, 5-25 min

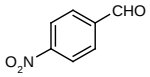
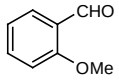
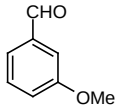
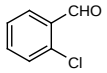
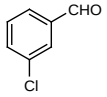
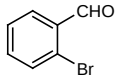
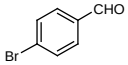
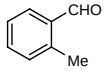
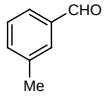
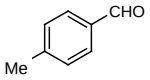
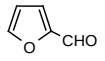
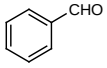
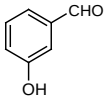
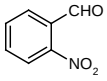
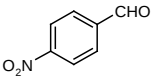
Next, acetylacetone was examined as substrate for the three component reaction. The pyran products **3a-j** were obtained in good to excellent yields (Table 2, entries 16-25). In summary, we have described an efficient one-pot, three-component reaction protocol for the synthesis of 2-amino-4H-pyran derivatives in aqueous media**.** Mild reaction conditions, operational simplicity, enhanced rates and high isolated yield of pure products are significant advantages of the described protocol. This reaction protocol conforms to several green chemistry principles coupled with the potential for developing combinatorial libraries.

Table 2. Synthesis of 2-amino-4H-pyrans in water- ethanol

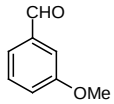
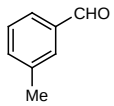
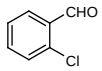
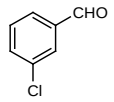
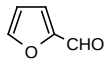


Entry	Aldehyde	Time, min	R	Product	Yield, % [a]	Mp (˚C)
1		5	OEt	**2a**	87	190-192 (lit.[25] mp 195-196)
2		10	OEt	**2b**	89	191-192 (lit.[25] mp 164-165)
3		5	OEt	**2c**	97 [b]	177.5-178.5
4		7	OEt	**2d**	79	187-188 (lit.[25] mp 182-183)

Contd…

5		5	OEt	**2e**	94	175-176 (lit.[25] mp 180-183)
6		25	OEt	**2f**	85	196-197
7		25	OEt	**2g**	86	147-148
8		20	OEt	**2h**	87	191-192
9		10	OEt	**2i**	92	180-180.5 (lit.[25] mp 153-156)
10		15	OEt	**2j**	89	183-184
11		10	OEt	**2k**	84	180-181
12		20	OEt	**2l**	86	140-141
13		20	OEt	**2m**	88	176-177
14		15	OEt	**2n**	83	175-176
15		25	OEt	**2o**	88	203-204
16		5	Me	**3a**	76	154.5-155.5
17		7	Me	**3b**	77	167-168
18		4	Me	**3c**	87	183-184
19		5	Me	**3d**	87	214-215
20		5	Me	**3e**	92	180-181

Contd…

21		20	Me	**3f**	86	180-181
22		17	Me	**3g**	74	191.5-192
23		15	Me	**3h**	87	143.5-144
24		8	Me	**3i**	86	194-195
25		20	Me	**3j**	71	180-181

[a] *Isolated yields after recrystallization.*

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