Synthesis of New 4-Substituted-3-alkoxy-2-butenoic Acid Esters and Pyrazole-3-one Derivatives

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Abstract

A number of new 4-substituted-3-alkoxy-2-butenoic acid esters have been synthesized through the reaction of ethyl (2\texttextsuperscript{E})-4-bromo-3-alkoxybut-2-enoates with phenols or naphthols in the presence of potassium carbonate and acetone. Treatment of these esters with hydrazine hydrate in ethanol afforded new pyrazol-3-one derivatives. The newly synthesized compounds were characterized by elemental analysis, NMR spectroscopy and mass spectrometry.

Keywords: 4-Substituted-3-alkoxy-2-butenoic acids; Pentadienoic acid; Pyrazol-3-one; Allylic bromination.

Introduction

2,4-Pentadienoic acids (1) are related, in their structures, to the plant hormone abscisic acid ABA (2). They have a wide spectrum pharmacological effect and several useful industrial applications. Some compounds are used as potential antimalarial agents \cite{1}, have retinoid-like biological activity \cite{2} while there are many examples were they are used as plant growth regulators \cite{3}. Certain derivatives are useful in industry as adhesive compounds \cite{4}.

Furthermore, it has been reported that some pentadienoic acids have growth inhibitory activity on rice seedlings \cite{5} and inhibit microbial growth storage in mango pulp \cite{6}. Other pentadienoic acids have been employed as plant antitranspirants either as free acids \cite{7} or as sodium or ammonium salts \cite{8}. Moreover, some pentadienoic acid derivatives are useful in the treatment of treatment of liver disorders \cite{9} whereas their salts are used as sunscreens \cite{10}. Some amide derivatives are useful in chemotherapy for the treatment of inflammation, atherosclerosis, restenosis, and immune disorders.

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such as arthritis and transplant rejection [11]. N-phenylethyl-5-phenyl-2,4-pentadienoicamides have been employed as blood platelet aggregation inhibitors [12].

Pyrazole containing compounds, on the other hand, exhibit a wide range of biological activities; some pyrazoles have been used as potential anticancer [13], anti-tumor [14], antibacterial [15], analgesic anti-inflammatory [16], antimicrobial cytotoxic agents [17], while others exhibited insecticidal [17a], herbicidal [17], antihypertensive [19], antipyretic [20], analgesic [20] and fungicidal [17] activities.

The most biologically active pyrazole compounds are certain pyrazole-3-ones that are inhibitors of tumor necrosis factor-α production and of the JNK3 kinase [21] or possess antihyperglycemic [22], antiproliferative [23], anti-tumor [24], or anti-angiogenic [25] properties. Additionally, the pyrazole-3-one ring is present in many naturally occurring compounds such as pseudoiodinine (3) [26], nostocine (4) [27] and withasomnine, 4-phenyl-1,5-trimethylenpyrazole (5), which was isolated from the roots of Indian medicinal plants of the species Withania somnifera Dun and its structure established by physical methods and total synthesis [28].

As part of our ongoing research on the synthesis of new compounds of pharmacological interest, we report herein the synthesis of new 4-substituted-3-alkoxy-2-butenolic acid esters and pyrazole-3-one derivatives which may exhibit useful biological activities. The 4-substituted-3-alkoxy-2-butenolic acid esters were synthesized through the reaction of ethyl (2E)-4-bromo-3-alkoxybut-2-enoate (9) with different aromatic compounds while the pyrazole-3-one derivatives were obtained from the reaction of the aforementioned esters with hydrazine hydrate.

**Experimental**

*Reagents*

Each of the following compounds was used without further purification:

ethyl acetoacetate (Riedel-de Haen), α-naphthol (Fluka), β-naphthol (s.d.fine Chemical, Ltd), 7-hydroxy-4-methylcoumarin (Aldrich), p-nitrophenol (Merck), p-tert-butylphenol (Fluka), p-methoxyphenol (Merck), p-hydroxybenzaldehyde (Riedel-de Haen), triethyl orthoformate (Riedel-de Haen), trimethyl orthoformate (Acros), N-bromosuccinimide (Acros), hydrochloric acid (Avonchem), potassium carbonate (Panreac).

*Instrumentation*

Melting points were measured with a Fischer-Johns melting point apparatus and were uncorrected. ¹H and ¹³C NMR were recorded with the aid of a Bruker-DPX 300 MHz spectrometer and are reported in ppm (δ) relative to TMS as an internal standard.
and with CDCl₃ or DMSO-d₆ as solvents. Mass spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200 °C. Elemental analyses were obtained using a Eurovector Euro EA3000, CHNS-O elemental analyzer. TLC was carried out using pre-coated silica gel (E. Merck Kiesegel 60 F₂₅₄ layer thickness 0.25 mm).

**Ethyl (2E)-3-alkoxybut-2-enoate (8):** (General procedure)

The title compound was synthesized according to the published procedure [29] by reacting ethyl acetoacetate (6) (13.0 g, 0.1 mol) with redistilled trimethyl orthoformate 7a (10.6 g, 0.1 mol) or triethyl orthoformate 7b (14.8 g, 0.1 mol) in absolute methanol (10 mL). Concentrated hydrochloric acid (0.05 mL) was added, and the mixture was immediately distilled to give ethyl (2E)-3-methoxybut-2-enoate (8a) (14.4 g, 99% yield) or ethyl (2E)-3-ethoxybut-2-enoate (8b) (14.2 g, 91% yield).

**Ethyl (2E)-4-bromo-3-alkoxybut-2-enoate (9)**

(General Procedure)

According to the procedure outlined by Pelter and coworkers [31] appropriate compound 8a,b (0.5 mol) was heated with vigorous stirring at 110-115 °C while N-bromosuccinimide (0.5 mol) was added in small portions. When addition was complete, the mixture was cooled to 70-80 °C and while vigorously stirring, water (125 mL) was added. The aqueous layer was separated and the organic layer was washed with water (3 x 35 mL), dried (MgSO₄), filtered, and distilled at once to give (90 g, 95%) 9a b.p. 135-138 °C/30 mmHg [lit.,31 132-136 °C/25 mmHg] or (91 g, 93%) 9b b.p. 139-143 °C/29 mmHg [lit.,31 137-142 °C/28 mmHg]

**Ethyl (2E)-3-alkoxy-4-aryloxybut-2-enoate (10)**

(General Procedure)

The appropriate phenol or naphthol (5.70 mmol) (Table 1) in acetone (50 mL) was stirred at room temperature for 15 min. To this mixture, solid potassium carbonate (0.87 g, 6.30 mmol) was added and the mixture was stirred at room temperature for 15 min followed by the addition of appropriate compound 9 (5.70 mmol). The mixture was refluxed for 24 h and the solid was filtered off. The solvent was either evaporated and the crude solid was recrystallized from ethanol, or was concentrated, extracted with dichlormethane/H₂O (3 X 100 mL), then the filtrate was dried (MgSO₄) and the solvent evaporated under reduced pressure to afford the appropriate product 10a-j. Using this general procedure the following compounds were synthesized:

**Ethyl (2E)-3-methoxy-4-(4-nitrophenoxy)but-2-enoate (10a)**

Yield = 76%, oil; ¹H NMR (300 MHz, CDCl₃): δ = 1.24 (t, J = 7.1 Hz, 3 H, CH₃-ester), 3.66 (s, 3 H, OMe), 4.13 (q, J = 7.1 Hz, 2 H, CH₂-ester), 5.21 (s, 1 H), 5.27 (s, 2 H), 6.99 (dd, J = 9.3, J = 4.9 Hz, 2 H), 8.14 (dd, J = 9.3 Hz, J = 4.9 Hz, 2 H). ¹³C NMR (300 MHz, CDCl₃): δ = 14.3 (CH₃), 56.2 (CH₃), 60.2 (CH₂), 65.2 (CH₂), 94.2 (CH),
Ethyl (2E)-3-ethoxy-4-(4-nitrophenoxy)but-2-enoate (10b)

Yield = 84%, mp. 65-67 °C; 1H NMR (300 MHz, CDCl3): δ = 1.25 (t, J = 7.1 Hz, 3 H, CH3-ester), 1.29 (t, J = 7.0 Hz, 3 H, OCH2CH3), 3.86 (q, J = 7.0 Hz, 2 H, O-CH2C=), 5.12 (s, 1 H, =CH), 7.00 (dd, J = 9.3, J = 4.9 Hz, 2 H), 8.16 (dd, J = 9.3, J = 4.9 Hz, 2 H). 13C NMR (300 MHz, CDCl3): δ = 14.0 (CH3), 14.3 (CH3), 60.1 (CH2), 64.8 (CH2), 65.4 (CH2), 94.3 (CH), 114.8 (CH), 125.9 (CH), 141.7 (C), 164.0 (C), 167.0 (C), 167.1 (C). MS (EI): m/z (%): 281 [M]+ (17), 236 (10) [M-45]+, 207 (6) [M-74]+, 176 (4) [M-105]+, 157 (5) [M-124]+, 129 (11) [M-152]+, 115 (96) [M-166]+, 98 (17) [M-183]+, 83 (60) [M-198]+, 55 (100) [M-226]+, 44 (90) [M-237]+.

Ethyl (2E)-3-methoxy-4-(4-methoxyphenoxy)but-2-enoate (10c)

Yield = 65%, oil; 1H NMR (300 MHz, CDCl3): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH3-ester), 3.57 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 4.07 (q, J = 7.1 Hz, 2 H, CH2-ester), 5.07 (s, 2 H, O-CH2C=), 5.10 (s, 1 H, =CH), 6.71 (dd, J = 9.1, J = 4.7 Hz, 2 H, Ar-H), 6.82 (dd, J = 9.1, J = 4.7 Hz, 2 H, Ar-H). 13C NMR (300 MHz, CDCl3): δ = 14.3 (CH3), 55.5 (CH3), 55.9 (CH3), 59.8 (CH2), 65.5 (CH2), 93.3 (CH), 114.5 (CH), 115.9 (CH), 152.6 (C), 154.1 (C), 166.8 (C), 169.6 (C). MS (EI): m/z (%): 295 [M]+ (94), 250 (72) [M-45]+, 220 (41) [M-75]+, 204 (41) [M-91]+, 192 (17) [M-103]+, 176 (28) [M-119]+, 157 (59) [M-138]+, 129 (83) [M-166]+, 115 (60) [M-180]+, 101 (100) [M-194]+, 83 (75) [M-212]+, 71 (86) [M-224]+, 55 (88) [M-240]+, 44 (73) [M-251]+. Anal. Calculated for C14H17NO6: C 56.94, H 5.80, N 4.74. Found: C 57.14, H 6.18, N 4.81 (%).

Ethyl (2E)-3-ethoxy-4-(4-methoxyphenoxy)but-2-enoate (10d)

Yield = 71%, oil; 1H NMR (300 MHz, CDCl3): δ = 1.24 (t, J = 7.1 Hz, 3 H, CH3-ester), 1.31 (t, J = 7.0 Hz, 3 H, OCH2CH3), 3.73 (s, 3 H, OMe), 3.84 (q, J = 7.0 Hz, 2 H, CH2-ester), 4.12 (q, J = 7.1 Hz, 2 H, CH2-ester), 5.11 (s, 2 H, O-CH2C=), 5.12 (s, 1 H, =CH), 6.87 (dd, J = 9.1, J = 4.7 Hz, 2 H), 6.89 (dd, J = 9.1, J = 4.7 Hz, 2 H). 13C NMR (300 MHz, CDCl3): δ = 14.1 (CH3), 14.4 (CH3), 55.7 (CH3), 59.8 (CH2), 64.5 (CH2), 65.8 (CH2), 93.7 (CH), 114.5 (CH), 126.1 (CH), 132.8 (C), 154.1 (C), 167.1 (C), 168.9 (C). MS (EI): m/z (%): 280 [M]+ (29), 235 (28) [M-45]+, 206 (7) [M-74]+, 191 (2) [M-89]+, 177 (12) [M-103]+, 157 (93) [M-129]+, 123 (100) [M-157]+, 101 (91) [M-179]+, 95 (67) [M-185]+, 77 (58) [M-203]+, 63 (37) [M-217]+, 55 (73) [M-225]+, 44 (56) [M-236]+. Anal. Calculated for C15H20O5: C 64.27, H 7.19. Found: C 64.42, H 7.43 (%).
Ethyl (2E)-4-(4-tert-butylphenoxy)-3-methoxybut-2-enoate (10e)

Yield = 55%, oil; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.27$ (m, 12 H, 3.68 (s, 3 H, OMe), 4.15 (q, $J = 7.1$ Hz, 2 H, CH$_2$-ester), 5.18 (s, 1 H, =CH), 5.19 (s, 2 H, O-CH$_2$C=), 6.89 (dd, $J = 8.7, J = 4.4$ Hz, 2 H), 6.82 (dd, $J = 8.7, J = 4.4$ Hz, 2 H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta = 14.4$ (CH$_3$), 31.6 (CH$_3$), 34.1 (C), 56.1 (CH$_3$), 59.9 (CH$_2$), 64.9 (CH$_2$), 93.3 (CH), 114.2 (CH), 126.2 (CH), 134.7 (C), 156.4 (C), 166.7 (CH). MS (EI): m/z (%): 292 [M]$^+$ (7), 277 (1) [M-15]$^+$, 247 (5) [M-45]$^+$, 231 (5) [M-61]$^+$, 217 (2) [M-75]$^+$, 203 (5) [M-89]$^+$, 157 (9) [M-135]$^+$, 143 (85) [M-149]$^+$, 135 (16) [M-157]$^+$, 115 (100) [M-177]$^+$, 102 (22) [M-190]$^+$, 83 (21) [M-209]$^+$, 55 (27) [M-237]$^+$.

Ethyl (2E)-4-(4-tert-butylphenoxy)-3-ethoxybut-2-enoate (10f)

Yield = 48%, oil; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.28$ (m, 12 H, CH$_3$), 3.85 (q, $J = 7.0$ Hz, 2 H, OCH$_2$CH$_3$), 4.15 (q, $J = 7.1$ Hz, 2 H, CH$_2$-ester), 5.16 (s, 1 H, =CH), 5.17 (s, 2 H, O-CH$_2$C=), 6.91 (dd, $J = 8.9, J = 4.5$ Hz, 2 H, Ar-H), 6.82 (dd, $J = 8.9, J = 4.5$ Hz, 2 H, Ar-H). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta = 14.1$ (CH$_3$), 14.4 (CH$_3$), 31.6 (CH$_3$), 34.1 (C), 59.9 (CH$_2$), 64.5 (CH$_2$), 65.1 (CH$_2$), 93.7 (CH), 114.4 (CH), 126.3 (CH), 134.6 (C), 156.5 (C), 167.1 (C), 168.9 (C). MS (EI): m/z (%): 306 [M]$^+$ (43), 291 (3) [M-15]$^+$, 261 (31) [M-45]$^+$, 245 (45) [M-61]$^+$, 231 (7) [M-75]$^+$, 217 (49) [M-89]$^+$, 203 (7) [M-103]$^+$, 189 (9) [M-117]$^+$, 176 (21) [M-130]$^+$, 157 (100) [M-149]$^+$, 147 (26) [M-159]$^+$, 135 (73) [M-171]$^+$, 129 (96) [M-177]$^+$, 115 (31) [M-201]$^+$, 101 (91) [M-205]$^+$, 91 (71) [M-215]$^+$, 73 (69) [M-233]$^+$, 55 (86) [M-251]$^+$.

Anal. Calculated for C$_{18}$H$_{26}$O$_4$: C 70.56, H 8.55. Found: C 70.14, H 8.89 (%).

Ethyl (2E)-3-ethoxy-4-(1-naphthyloxy)but-2-enoate (10g)

Yield = 52%, oil; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.23$ (t, $J = 7.1$ Hz, 3 H, CH$_3$-ester), 1.30 (t, $J = 7.0$ Hz, 3 H, OCH$_2$CH$_3$), 3.88 (q, $J = 7.0$ Hz, 2 H, OCH$_2$CH$_3$), 4.17 (q, $J = 7.1$ Hz, 2 H, CH$_2$-ester), 5.20 (s, 1 H, =CH), 5.27 (s, 2 H, O-CH$_2$C=), 6.85-7.32 (m, 7 H, naphthalene protons). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta = 14.0$ (CH$_3$), 14.4 (CH$_3$), 59.9 (CH$_2$), 64.6 (CH$_2$), 65.9 (CH$_2$), 93.6 (CH), 114.2 (CH), 121.9 (CH), 123.2 (CH), 125.6 (CH), 126.3 (CH), 126.6 (CH), 127.7 (C), 130.2 (CH), 134.6 (C), 154.2 (C), 186.2 (C). MS (EI): m/z (%): 300 [M]$^+$ (20), 254 (25) [M-46]$^+$, 226 (12) [M-74]$^+$, 197 (15) [M-103]$^+$, 181 (20) [M-192]$^+$, 157 (97) [M-143]$^+$, 144 (45) [M-156]$^+$, 129 (98) [M-171]$^+$, 115 (99) [M-185]$^+$, 101 (100) [M-199]$^+$, 73 (61) [M-227]$^+$, 44 (87) [M-256]$^+$.

Anal. Calculated for C$_{18}$H$_{20}$O$_4$: C 71.98, H 6.71. Found: C 71.98, H 6.71 (%).

Ethyl (2E)-3-ethoxy-4-(2-naphthyloxy)but-2-enoate (10h)

Yield = 75%, oil; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.25$-1.34 (m, 6 H, Ar-H), 3.82 (q, $J = 7.0$ Hz, 2 H, OCH$_2$CH$_3$), 4.12 (q, $J = 7.1$ Hz, 2 H, CH$_2$-ester), 5.12 (s, 1 H, =CH), 5.27 (s, 2 H, O-CH$_2$C=), 7.19-7.76 (m, 7 H, naphthalene protons). $^{13}$C NMR (300 MHz, CDCl$_3$): $\delta = 14.1$ (CH$_3$), 14.4 (CH$_3$), 60.0 (CH$_2$), 64.7 (CH$_2$), 65.1 (CH$_2$), 93.9 (CH), 215
107.4 (CH), 119.1 (CH), 123.6 (CH), 126.3 (CH), 126.8 (CH), 127.4 (CH), 129.4 (C), 129.6 (CH), 134.5 (C), 156.4 (C), 167.2 (C), 168.6 (C). MS (EI): m/z (%): 300 [M]+ (38), 254 (32) [M-46]+, 226 (8) [M-74]+, 197 (10) [M-103]+, 181 (24) [M-192]+, 157 (100) [M-143]+, 144 (38) [M-156]+, 129 (93) [M-171]+, 115 (75) [M-185]+, 101 (79) [M-199]+, 73 (22) [M-227]+, 55 (21) [M-245]+, 44 (16) [M-256]+. Anal. Calculated for C18H20O4: C 71.98, H 6.71. Found: C 71.52, H 6.93(%) .

Ethyl (2E)-3-methoxy-4-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]but-2-enoate (10i)

Yield = 67%, mp. 101-102 °C; 1H NMR (300 MHz, CDCl3): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH3-ester), 2.36 (s, 3 H, 4-CH3), 3.37 (s, 3 H, OMe), 4.17 (q, J = 7.1 Hz, 2 H, CH2-ester), 5.20 (s, 1 H, =CH), 5.25 (s, 2 H, O-CH2C=), 6.10 (s, 1 H, H-3), 6.87 (m, 2 H, H-5 and H-6), 7.46 (d, J = 8.70 Hz, 1 H, H-8). 13C NMR (300 MHz, CDCl3): δ = 16.4 (CH3), 18.7 (CH3), 56.2 (CH3), 60.1 (CH2), 65.1 (CH2), 94.0 (CH), 102.0 (CH), 112.1 (CH), 112.5 (CH), 114.0 (C), 125.6 (CH), 152.6 (C), 155.2 (C), 161.4 (C), 161.6 (C), 166.8 (C), 168.2 (C). MS (EI): m/z (%): 318 (5) [M]+, 273 (7) [M-45]+, 240 (8) [M-78]+, 176 (3) [M-142]+, 157 (26) [M-161]+, 143 (49) [M-175]+, 115 (100) [M-203]+, 83 (69) [M-235]+, 63 (90) [M-255]+. Anal. Calculated for C17H18O6: C, 64.14; H, 5.70. Found: C, 64.48; H, 5.96 (%).

Ethyl (2E)-3-ethoxy-4-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]but-2-enoate (10j)

Yield = 79%, mp. 97-98 °C; 1H NMR (300 MHz, CDCl3): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH3-ester), 1.27 (t, J = 7.0 Hz, 3 H, OCH2CH3), 2.33 (s, 3 H, 4-CH3), 3.83 (q, J = 7.0 Hz, 2 H, CH2-ester), 4.11 (q, J = 7.1 Hz, 2 H, CH2=ester), 5.15 (s, 1 H, =CH), 5.21 (s, 2 H, O-CH2C=), 6.07 (s, 1 H, H-3), 6.86 (m, 2 H, H-5 and H-6), 7.74 (d, J = 8.70 Hz, 1 H, H-8). 13C NMR (300 MHz, CDCl3): δ = 16.0 (CH3), 16.3 (CH3), 18.7 (CH3), 60.0 (CH2), 64.7 (CH2), 65.4 (CH2), 94.2 (CH), 102.0 (CH), 112.1 (CH), 112.5 (CH), 113.9 (C), 125.5 (CH), 152.1 (C), 155.1 (C), 161.4 (C), 161.7 (C), 166.9 (C), 167.4 (C). MS (EI): m/z (%): 332 (67) [M]+, 287 (57) [M-45]+, 258 (33) [M-74]+, 240 (63) [M-92]+, 216 (56) [M-116]+, 189 (43) [M-143]+, 157 (95) [M-175]+, 129 (98) [M-203]+, 101 (100) [M-231]+, 73 (74) [M-259]+. Anal. Calculated for C18H20O6: C, 65.05; H 6.07. Found: C, 65.14; H, 5.74 (%).

5-[(Aryloxy)methyl]-1,2-dihydro-3H-pyrazol-3-one (11): (General Procedure)

A solution of hydrazine hydrate 98% (0.05 g, 1.00 mmol) in absolute ethanol (20 mL) was added dropwise to the appropriate compound 10a-f (1.00 mmol) and the resulting mixture was heated to reflux for 48 h. The reaction mixture was allowed to cool to room temperature and then further cooled with ice-water and the resulting solid filtered to give compounds 11a-f.
5-[(4-Nitrophenoxy)methyl]-1,2-dihydro-3H-pyrazol-3-one (11a)
Yield = 50%, mp. 230-233 °C; ¹H NMR (300 MHz, DMSO-d₆): δ = 5.05 (s, 2 H, O-CH₂C=), 5.52 (s, 1 H, =CH), 7.17 (dd, J = 9.3, J = 5.1 Hz, 2 H, Ar-H), 8.16 (dd, J = 9.3, J = 5.1 Hz, 2 H, Ar-H), 10.8 (br, s, 2 H, NH). ¹³C NMR (300 MHz, DMSO-d₆): δ = 62.4 (CH₂), 90.3 (CH), 115.8 (CH), 126.3 (CH), 140.8 (C), 141.4 (C), 159.1 (C), 163.8 (C). MS (EI): m/z (%): 235 [M⁺] (26), 139 (60) [M-96]⁺, 123 (29) [M-112]⁺, 109 (39) [M-126]⁺, 97 (100) [M-138]⁺, 81 (21) [M-154]⁺, 67 (64) [M-168]⁺, 53 (22) [M-182]⁺. Anal. Calculated for C₁₀H₉N₃O₄: C 51.07, H 3.86, N 17.87. Found C 50.86, H 4.23, N 17.25 (%).

5-[(4-Methoxyphenoxy)methyl]-1,2-dihydro-3H-pyrazol-3-one (11b)
Yield = 70%, mp. 229-233 °C; ¹H NMR (300 MHz, DMSO-d₆): δ = 3.65 (s, 3 H, OCH₃), 4.81 (s, 2 H, O-CH₂C=), 5.45 (s, 1 H, =CH), 6.81 (dd, J = 9.2, J = 4.3 Hz, 2 H, Ar-H), 6.89 (dd, J = 9.2, J = 4.3 Hz, 2 H, Ar-H), 9.90 (br, s, 1 H, NH), 11.7 (br, s, 1 H, NH). ¹³C NMR (300 MHz, DMSO-d₆): δ = 55.8 (CH₃), 62.5 (CH₂), 89.8 (CH), 115.0 (CH), 116.2 (CH), 140.9 (C), 152.5 (C), 154.0 (C), 160.9 (C). MS (EI): m/z (%): 220 [M⁺] (28), 124 (100) [M-96]⁺, 109 (39) [M-111]⁺, 97 (34) [M-123]⁺, 81 (15) [M-139]⁺, 67 (42) [M-153]⁺, 52 (12) [M-168]⁺. Anal. Calculated for C₁₁H₁₂N₂O₃: C 59.99, H 5.49, N 12.72. Found C 59.95, H 5.21, N 12.89 (%).

5-[(4-tert-Butylphenoxy)methyl]-1,2-dihydro-3H-pyrazol-3-one (11c)
Yield = 70%, mp. 242-244 °C; ¹H NMR (300 MHz, DMSO-d₆): δ = 1.21 (s, 9 H, CH₃), 4.86 (s, 2 H, O-CH₂C=), 5.47 (s, 1 H, =CH), 6.87 (dd, J = 8.8, J = 4.7 Hz, 2 H, Ar-H), 7.25 (dd, J = 8.8, J = 4.7 Hz, 2 H, Ar-H), 10.0 (br, s, 1 H, NH), 11.8 (br, s, 1 H, NH). ¹³C NMR (300 MHz, DMSO-d₆): δ = 31.8 (CH₃), 34.3 (C), 62.1 (CH₂), 89.7 (CH), 114.7 (CH), 126.5 (CH), 140.9 (C), 143.4 (C), 156.3 (C), 160.9 (C). MS (EI): m/z (%): 246 [M⁺] (38), 231 (5) [M-15]⁺, 190 (5) [M-56]⁺, 150 (51) [M-96]⁺, 136 (100) [M-110]⁺, 115 (12) [M-131]⁺, 107 (41) [M-139]⁺, 97 (49) [M-149]⁺, 77 (35) [M-169]⁺, 67 (47) [M-179]⁺, 55 (22) [M-191]⁺. Anal. Calculated for C₁₄H₁₈N₂O₂: C 68.27, H 7.37, N 11.37. Found C 70.14, H 7.63, N 11.70 (%).

5-[(1-Naphthyloxy)methyl]-1,2-dihydro-3H-pyrazol-3-one (11d)
Yield = 56%, mp. 245-245 °C; ¹H NMR (300 MHz, DMSO-d₆): δ = 4.89 (s, 2 H, O-CH₂C=), 6.57 (s, 1 H, =CH), 7.18-8.00 (m, 7 H, aromatic protons), 11.6 (br, s, 2 H, NH). ¹³C NMR (300 MHz, DMSO-d₆): δ = 62.9 (CH₂), 89.6 (CH), 105.6 (CH), 120.8 (CH), 122.0 (CH), 125.3 (CH), 125.7 (CH), 126.5 (CH), 126.9 (CH), 127.9 (C), 134.5 (C), 140.9 (C), 153.9 (C), 160.2 (C). MS (EI): m/z (%): 240 [M⁺] (31), 144 (100) [M-96]⁺, 127 (16) [M-113]⁺, 115 (46) [M-125]⁺, 97 (41) [M-143]⁺, 78 (15) [M-162]⁺, 63 (37) [M-177]⁺, 55 (8) [M-185]⁺. Anal. Calculated for C₁₄H₁₂N₂O₂: C 69.99, H 5.03, N 11.66. Found C 69.72, H 5.14, N 11.53 (%).
5-[(2-Naphthyloxy)methyl]-1,2-dihydro-3H-pyrazol-3-one (11e)

Yield = 80%, mp. 245-248 °C; ¹H NMR (300 MHz, DMSO-d₆): δ = 5.01 (s, 2 H, O-CH₂C=), 5.56 (s, 1 H, =CH), 7.14-7.81 (m, 7 H, aromatic protons), 11.7 (br, s, 2 H, NH). ¹³C NMR (300 MHz, DMSO-d₆): δ = 62.1 (CH₂), 90.9 (CH), 107.6 (CH), 119.2 (CH), 124.2 (CH), 126.9 (CH), 127.2 (CH), 128.0 (CH), 128.2 (C), 129.8 (CH), 134.7 (C), 141.1 (C), 156.4 (C), 160.6 (C). MS (EI): m/z (%): 240 [M]+ (31), 144 (100) [M-96]+, 127 (12) [M-113]+, 115 (82) [M-125]+, 97 (62) [M-143]+, 78 (12) [M-162]+, 63 (46) [M-177]+, 55 (15) [M-185]+. Anal. Calculated for C₁₄H₁₂N₂O₂: C 69.99, H 5.03, N 11.66. Found C 69.81, H 5.08, N 11.45 (%).

5-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]methyl]-1,2-dihydro-3H-pyrazol-3-one (11f)

Yield = 64%, mp. 234-237 °C; ¹H NMR (300 MHz, DMSO-d₆): δ = 2.13 (s, 3 H, 4-CH₃), 5.00 (s, 2 H, O-CH₂C=), 5.53 (s, 1 H, =CH), 6.07 (s, 1 H, H-3), 6.97 (m, 2 H, H-5 and H-6)), 7.58 (d, J = 8.8 Hz, 1 H, H-8), 10.8 (br, s, 2 H, NH). ¹³C NMR (300 MHz, DMSO-d₆): δ = 18.6 (CH₃), 62.4 (CH₂), 90.2 (CH), 102 (CH), 111.7 (CH), 113.1 (C), 113.7 (CH), 126.9 (CH), 140.7 (C), 153.8 (C), 155.1 (C), 159.4(C), 160.6 (C), 161.5 (C). MS (EI): m/z (%): 272 [M]+ (35), 176 (100) [M-96]+, 148 (96) [M-124]+, 120 (23) [M-152]+, 97 (85) [M-175]+, 77 (36) [M-195]+, 65 (51) [M-207]+, 55 (12) [M-15]+. Anal. Calculated for C₁₄H₁₂N₂O₄: C 61.76, H 4.44, N 10.29. Found C 61.44, H 4.74, N 9.90(%) .

Results and discussion

The starting material, ethyl (2E)-3-alkoxybut-2-enoate 8a,b, can be efficiently synthesized according to the literature [29] from the reaction between ethyl acetoacetate 6 with an equimolar amount of the corresponding redistilled trimethyl orthoformate 7a or triethyl orthoformate 7b, followed by the addition of concentrated hydrochloric acid and immediate distillation to give 8a (99%) or 8b (91%), respectively. Allylic bromination of compounds 8a,b using N-bromosuccinimide afforded the corresponding ethyl (2E)-4-bromo-3-alkoxybut-2-enoates 9a,b. Reaction of 9 with the appropriate phenol or naphthol (Table 1) in acetone and in the presence of potassium carbonate led to the formation of ethyl (2E)-3-alkoxy-4-aryloxybut-2-enoate (10). Negi and coworkers [30] have used a similar procedure to prepare a plant growth promoter from gallic acid; the desired product was obtained by reacting (2-hydroxynaphthalen-1-yl)-(3,4,5-trimethoxyphenyl)methanone with ethyl bromocrotonate in dry acetone and in the presence of potassium carbonate. The product obtained has shown potent auxin[30] like growth promoter activity. The steps involved in the synthesis of 8 are depicted in Scheme 1. On the other hand, reaction of 10 with hydrazine hydrate in ethanol yielded a number of new 5-(aryloxymethyl)-1,2-dihydro-3H-pyrazol-3-one derivatives (11) (Scheme 1).
Table 1. Synthesis of ethyl (2E)-3-alkoxy-4-aryloxybut-2-enoate (10) and 5-(aryloxymethyl)-1,2-dihydro-3H-pyrazol-3-one derivatives (11) according to Scheme 1.

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</tr>
<tr>
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<td>CH₃</td>
<td>p-CH₃OC₆H₄ -</td>
</tr>
<tr>
<td>7c</td>
<td>CH₃</td>
<td>p-BuOC₆H₄ -</td>
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</tr>
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<td>4-methyl-2-oxo-2H-chromen-7-yl-</td>
</tr>
<tr>
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<td>4-methyl-2-oxo-2H-chromen-7-yl-</td>
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<tr>
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</tr>
<tr>
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¹H NMR and ¹³C NMR spectra of the all prepared compounds are in total agreement with the suggested structures; DEPT experiments were employed to differentiate between secondary and quaternary carbons from primary and tertiary carbons. Mass spectral data of compounds are also in agreement with the assigned structures and show the expected molecular ions.
The $^1$H NMR spectra of compounds 10a, 10c, 10e, and 10i showed, in addition to the aromatic protons, a triplet at δ 1.18-1.24 ppm ($J = 7.1$ Hz), a singlet at δ 3.37-3.68 ppm, a quartet at δ 4.07-4.15 ppm ($J = 7.1$ Hz), and two singlets at δ 5.10-5.21 ppm and δ 5.07-5.27 ppm. The $^{13}$C-NMR spectra of the aforementioned compounds indicate the presence of a methyl signal at δ 13.8-14.4 ppm, a methoxy methyl signal at δ 55.5-56.2 ppm, an ester CH$_2$ signal at δ 59.7-65.1 ppm, an ether CH$_2$ signal at δ 60.1-65.5 ppm, a CH signal at δ 93.3-94.2 ppm, a carbonyl ester carbon signal at δ 163.6-166.9 ppm, and a quaternary carbon signal at δ 167.4-169.7 ppm.

Similarly, the $^1$H NMR spectra of compounds 10b, 10d, 10f, 10g, 10h, and 10k indicated, in addition to the aromatic protons, a triplet signal at δ 1.00-1.55 ppm ($J = 7.0$ Hz) attributed to the ester -OCH$_2$CH$_3$ methyl protons, a triplet at δ 1.18-1.24 ppm ($J = 7.1$ Hz), due to the ether -OCH$_2$CH$_3$ methyl protons, a quartet at δ 3.83-3.86 ppm ($J = 7.1$ Hz) and a quartet at δ 3.91-4.17 ppm ($J = 7.0$ Hz) attributed to the ether -OCH$_2$CH$_3$ and to the ester -OCH$_2$CH$_3$ methylene protons, respectively. The vinylic proton appears as a singlet at δ 5.05-5.30 ppm. The $^{13}$C NMR spectra of these compounds showed the expected number of carbon signals.

$^1$H NMR and $^{13}$C NMR spectra of the prepared pyrazole-3-one derivatives were also in agreement with the assigned structures. The NH protons appear as a broad singlet of two protons intensity at δ 9.9-11.7 ppm.

References


