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INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF 3-CARBOMETHOXY-2-PYRONES WITH 1,1-DIMETHOXYETHYLENE: A SIMPLE AND MILD METHOD OF ARYL ANNULATION

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Abstract: A simple process for aryl annulation based on the inverse electron demand Diels-Alder reaction of 5,6-substituted-3-carbomethoxy-2-pyrones with 1,1-dimethoxyethylene is described.

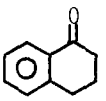
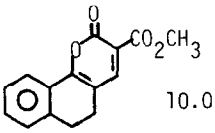
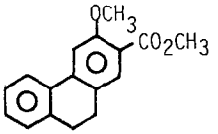
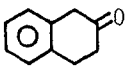
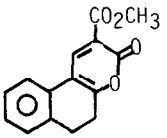
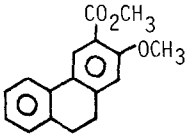
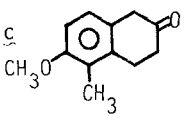
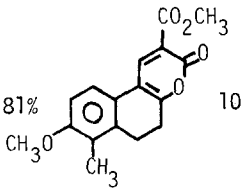
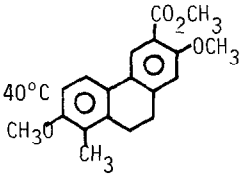
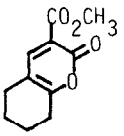
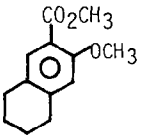
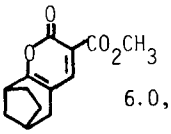
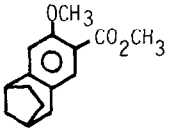
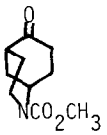
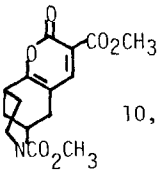
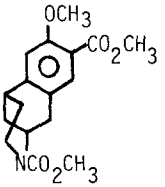
The use of α-pyrones in Diels-Alder reactions with electron deficient dienophiles for the preparation of dienes and aromatic systems has been thoroughly explored and often is found implemented successfully into the solution of synthetic problems.[2] In contrast, the potential for α-pyrones to behave as dependable, electron deficient dienes in an inverse electron demand Diels-Alder reaction with electron rich dienophiles has not been fully realized and, with a few notable exceptions, has not been widely employed.[3]

In the course of synthetic studies detailed in the accompanying communications, we have had the occasion to investigate useful methods for the introduction of an aryl ring. These studies have focused principally on the annulation of an aryl ring onto a preexisting ketone, equation 1.[4]

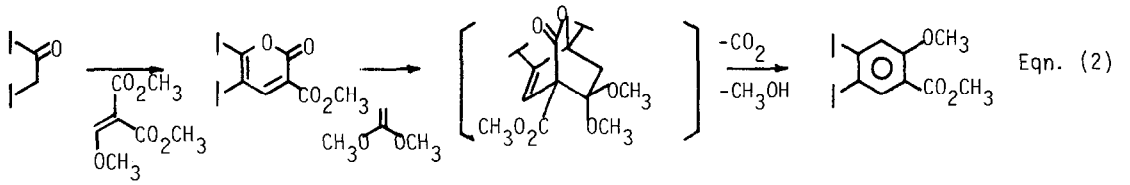
Eqn. (1)

Herein, we would like to describe an additional complementary and simple process for salicylate/phenol[5] annulation based on the observation that α-pyrones substituted with an electron withdrawing group may participate in cycloaddition reactions with electron rich dienophiles.[3] The two-step sequence requires conversion of a ketone (1) to the substituted 3-carbomethoxy-2-pyrone 3 followed by a regiospecific, thermal cycloaddition of 3 with the electron rich dienophile, 1,1-dimethoxyethylene (4), providing the annulated salicylate 5, equation 2.

Table I. Salicylate Annulation.

	Ketone 1	3-Carbomethoxy-2-pyrone 3 Method, % Yield[a]	Conditions equiv. 4 solvent, time, temp.	Product 5[a]	% Yield
a		B, 90% 	10.0, toluene, 15 h, 120°C		78%
b		A, 73% 	9.0, toluene 22 h, 140°C	 [b]	59%
c	 [c]	A, 81% 	10.0, toluene, 21 h, 140°C	 [c]	75%
d		B, 84% 	5.5, toluene, 15 h, 95°C	 [d]	78%
e		B, 62% 	6.0, toluene, 12 h, 95°C		90%
f	 [e]	B, 47% 	10, toluene, 13 h, 120°C		80%

(a) All products exhibited the reported or expected ^{1}H-NMR, IR, and mass spectral characteristics. All new compounds gave satisfactory elemental analysis (±0.40%) or high resolution mass spectral information. All yields are based on purified product isolated by column chromatography (SiO_2). (b) Mosettig, E.; Stuart, A. H. J. Am. Chem. Soc. 1939, 61, 1. (c) Boger, D. L.; Mullican, M. D. accompaning communication. (d) Arnold, R. T.; Zaugg, H. E.; Sprung, J. J. Am. Chem. Soc. 1941, 63, 1314. (e) Boger, D. L.; Patel, M.; Mullican, M. D. accompaning communication.



Eqn. (2)

1 2 3 4 5

Table I details the results of this investigation. Treatment of a ketone enolate, generated with sodium hydride (Method A) or lithium diisopropylamide (Method B), with dimethyl methoxymethylenemalonate (2)[6] provides the substituted 3-carbomethoxy-2-pyrones directly (45-90%). The Diels-Alder reaction of the substituted 3-carbomethoxy-2-pyrones 3 with 1,1-dimethoxyethylene (4) occurs under mild conditions (5-10 equiv. 4, 90-140°C, toluene) with complete regiospecificity and is accompanied by the loss of carbon dioxide and in situ loss of methanol to provide the salicylate product 5 directly, (60-90%, Table I).

The simplicity of this sequence, the unusual potential for the appropriate choice of α-pyrone or alternative electron rich dienophiles indicates that this initial observation is capable of broad and general application. The use of this salicylate preparation in the synthesis of juncusol and representative synthetic analgesics is described in the following communications. Typical experimental procedures are detailed below.

3-Carbomethoxy-2-pyrone 3b: Method A. A solution of β-tetralone (1.10 g, 7.56 mmol) in 9 ml of THF was added dropwise (15 min.) to a slurry of NaH (670 mg of 60% in oil, 16.75 mmol, 2.20 equiv.) in 20 ml of THF at 0°C under argon. Dimethyl methoxymethylenemalonate (2[6], 1.58 g, 9.07 mmol, 1.20 equiv.) in 8 ml of THF was added over 15 min. at 0°C and the resulting reaction was stirred at 0° to 25°C for 3 h before being poured onto cold aq. 5% HCl (40 ml) and extracted with $CHCl_3$ (7 x 20 ml). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (50 g SiO_2, 30 x 2 cm, 50 to 100% ether-hexane eluant) yielded 1.42 g (1.94 g theor., 73%) of α-pyrone 3b as a yellow solid: m.p. 129-130°C (EtOAc); ^{1}H-NMR ($CDCl_3$) δ 8.70 (s, 1H), 7.55-7.10 (m, 4H), 3.94 (s, 3H), 3.00 (d, J = 7 Hz, 2H), 2.94 (d, J = 7 Hz, 2H); IR ($CHCl_3$) ν_{max} 3020, 2960, 1750, 1710, 1545, 1250, 1095, 1005 cm^{-1}; mass spectrum, m/e (rel. intensity) 256 (M^+, base), 255 (2), 254 (12), 228 (24), 225 (16), 224 (39), 196 (13), 169 (23), 168 (12), 155 (10), 141 (34), 140 (19), 139 (30), 128 (11), 127 (10), 115 (29), 63 (12); HRMS, m/e 256.0719 ($C_{15}H_{12}O_4$ requires 256.0735).

3-Carbomethoxy-2-pyrone 3d: Method B. A solution of cyclohexanone (0.40 ml, 380 mg, 3.9 mmol) in 5 ml of THF was added dropwise (15 min.) to a -78°C solution of freshly generated lithium diisopropylamide (4.6 mmol, 1.2 equiv.) in 10 ml of THF and the resulting mixture was stirred at -78°C to -5°C over 1.75 h. The solution was recooled to -30°C and dimethyl methoxymethylenemalonate (2[6], 810 mg, 4.6 mmol, 1.2 equiv.) in 2 ml of THF was added dropwise (15 min.). The resulting mixuture was stirred at -30°to 25°C for 2.75 h before being poured onto 5% aq. HCl (30 ml) and extracted with CH_2Cl_2 (5 x 20 ml). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 16 x 1.5 cm, 50% ether-hexane eluant) gave 680 mg (812 mg theor., 84% yield) of α-pyrone 3d as a white solid: m.p. 107°-108°C (EtOAc/hexane); ^{1}H-NMR ($CDCl_3$) δ 7.99 (s, 1H, vinyl) 3.86 (s, 3H, $-CO_2CH_3$), 2.46 (m, 4H), 1.80 (m, 4H); IR ($CHCl_3$) ν_{max} 3040, 2975, 1765, 1745, 1555, 1445, 1370, 1300, 1270, 1220, 1155, 1095, 880 cm^{-1}; mass spectrum, m/e (rel. intensity) 208 (M^+, 68), 181 (6), 180 (48), 177 (35), 176 (18), 152 (58), 149 (25), 148 (33), 124 (11), 122 (14), 121 (base), 120 (33), 91 (32), 79 (19), 72 (25), 65 (21); Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.79; H, 5.94.

Methyl 3-methoxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate (5d): 3-Carbomethoxy-2-pyrone (3d, 179 mg, 0.86 mmol), 1,1-dimethoxyethylene (4, 0.45 ml, 0.41 g, 4.7 mmol, 5.5 equiv.), and toluene (1.0 ml) were combined at 25°C under argon and warmed at 95°C for 15 h. Chromatography (SiO_2, 14.5 x 1.5 cm, 30% ether-hexane eluant) afforded 147 mg (189 g theor., 78%) of 5d as a white solid: m.p. 98.5-99.5°C (lit.[7] m.p. 99-100°C); ^{1}H-NMR ($CDCl_3$) δ 7.53 (s, 1H), 6.65 (s, 1H), 3.86 (s, 6H), 2.90-2.55 (m, 4H), 1.90-1.70 (m, 4H); IR ($CHCl_3$) ν_{max} 3000, 2940, 1710, 1600, 1490, 1420, 1260, 1175, 1060 cm^{-1}; mass spectrum, m/e (rel. intensity) 220 (M^+, 75), 219 (3), 205 (1), 203 (2), 191 (16), 190 (15), 189 (base), 188 (13), 187 (69), 161 (51), 159 (17), 131 (19), 129 (12), 128 (10), 117 (16), 116 (11), 115 (28), 105 (12), 91 (35), 89 (10), 77 (18), 63 (10).

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