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General Strategy for the Synthesis of Natural and Unnatural Dialkylmaleic Anhydrides

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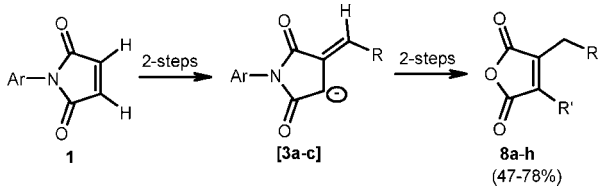
Received June 16, 2008



Starting from alkylidenesuccinimides, a wide range of dialkylmaleic anhydrides have been synthesized via the generation of a carbanion on a succinimide unit and its condensation with various alkyl halides as the key reaction.

The cyclic anhydride is one of the important functionalities in chemistry and has been used to design a variety of bioactive natural products, structurally interesting heterocyclic systems, and polymers with tailored material characteristics.[1] To date, several dialkylmaleic anhydrides have also been isolated as potent bioactive natural products[2,3] and many product specific syntheses with some limitations are known in the literature.[4,5] Now, we herein report a general strategy for the synthesis of a wide range of natural and unnatural dialkylmaleic anhydrides.

It is well established that maleimides couple with triphenylphosphine to generate an in situ Wittig reagent, which on reaction with a variety of aldehydes provide the corresponding thermodynamically more stable (*E*)-alkylidenesuccinimides in decent yields.[6] The exclusive formation of (*E*)-isomers in products **2a**−**c** was established on the basis of the lower field ^{1}H NMR resonance for the vinylic proton in close proximity to the carbonyl and was further confirmed by comparing with similar known compounds.[5t] Recently, we have proved that the alkylidenesuccinimides are thermodynamically more stable than the corresponding alkylmaleimides and hence a direct prototropic shift with an exocyclic to endocyclic double bond migration is impossible.[7] We reasoned and planned to take advantage of this observation by studying the feasibility of generation of an allylic carbanion on the alkylidenesuccinimide nucleus and further explore its condensation reactions with a variety of alkyl halides to develop a new general approach to dialkyl maleimides and maleic anhydrides.

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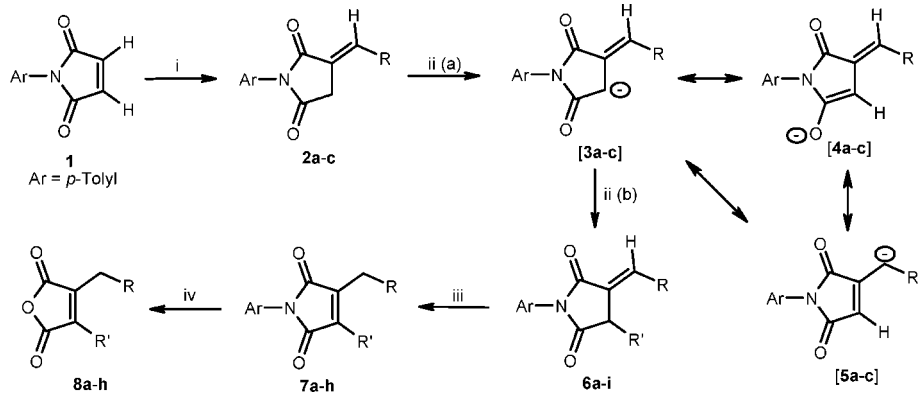
10.1021/jo801284r CCC: $40.75
Published on Web 07/30/2008

TABLE 1. Synthesis of Natural and Unnatural Dialkylmaleic Anhydrides[a]

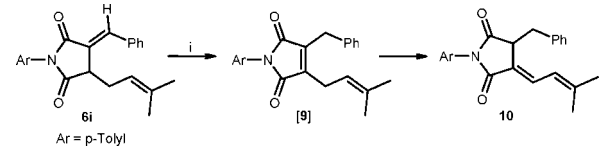


entry	RCHO	product **2** (% yield)	R′X	product **6** (% yield)	product **7** (% yield)	product **8** (% yield)
1	$CH_3(CH_2)_4CHO$	**2a** (91)	EtO_2CCH_2Br	**6a** (70)	**7a** (92)	**8a** (88)[d]
2	$CH_3(CH_2)_4CHO$	**2a** (91)	$EtO_2CCH_2CH_2Br$	**6b** (−)[b]	**7b** (70)[c]	**8b** (85)[d]
3	$CH_3(CH_2)_4CHO$	**2a** (91)	$CH_3(CH_2)_4CH_2Br$	**6c** (72)	**7c** (98)	**8c** (90)[f]
4	$CH_3(CH_2)_4CHO$	**2a** (91)	$PhCH_2Br$	**6d** (80)	**7d** (93)	**8d** (97)[f]
5	$CH_3(CH_2)_{12}CHO$	**2b** (89)	CH_3I	**6e** (65)	**7e** (90)	**8e** (91)[d]
6	PhCHO	**2c** (93)	$PhCH_2Br$	**6f** (87)	**7f** (94)	**8f** (97)[e]
7	PhCHO	**2c** (93)	$(CH_3)_2CHI$	**6g** (92)	**7g** (98)	**8g** (94)[e]
8	PhCHO	**2c** (93)	CH_3I	**6h** (68)	**7h** (92)	**8h** (89)[f]
9	PhCHO	**2c** (93)	$(CH_3)_2C{=}CHCH_2Br$	**6i** (85)		

[a] Reagents and conditions: (i) Ph_3P (1.00 equiv), RCHO (1.50 equiv), THF, reflux, 10 h (89−93%); (ii) (a) NaH (1.00 equiv), THF, 0 °C, 0.5 h, (b) R′X (1.00 equiv), 0 °C to rt, 3 h (65−92%); (iii) Et_3N + THF (1:1), reflux, 48 h (90−98%); (iv) (a) THF + MeOH (1:2), KOH, H_2O, reflux, 2 h, (b) H^+/HCl (85−97%). [b] Not isolated as both the starting material 2a and the product 6b were having the same R_f value. [c] Yield over two steps. [d] Natural products. [e] Natural product precursors. [f] Unnatural analogues.

In alkylidenesuccinimides **2a**−**c** the methylene protons are acidic because of the adjacent imide carbonyl group and their allylic nature. As per our hypothesis, the alkylidenesuccinimides **2a**−**c** on treatment with an equivalent amount of sodium hydride in THF at 0 °C turned into a deep red solution, indicating the formation of the carbanion. The reactions of the above carbanionic solutions with simple alkyl halides, activated alkyl halides, allylic alkyl halides, and benzyl halides at 0 °C exclusively furnished the corresponding desired ring monoalkylated products **6a**−**i** in 65−92% yields (Table 1). Herein also the (*E*)-geometry of the exocyclic carbon−carbon double bond in products **6a**−**i** was confirmed on the basis of ^{1}H NMR data. These observations clearly revealed that the alkylidenesuccinimidoyl carbanionic species **3a**−**c** can be in resonance with intermediates **4a**−**c** and alkylmaleimidoyl carbanionic species **5a**−**c**. We feel that the resonance hybrid prefers to react with alkyl halides via the relatively more contributing carbanionic species **3a**−**c** rather than the carbanionic species **5a**−**c** to form the products **6a**−**i**. With the introduction of suitable alkyl substituents on **2a**−**c** to form **6a**−**i**, the trisubstituted exocyclic to tetrasubstituted endocyclic carbon−carbon double bond isomerization became feasible on treatment of **6a**−**h** with triethylamine to obtain **7a**−**h** in 70−98% yields. Interestingly, the alkylsuccinimide **6i** on treatment with triethylamine underwent two successive prototropic shifts to exclusively yield the thermodynamically more stable alkylidenesuccinimide **10** via the unisolable dialkyl maleimide intermediate **9** (Scheme 1). In the conversion of **6i** to **10**, the loss of conjugation with the phenyl ring and subsequent gain of conjugation with the acyclic carbon−carbon double bond indicates that the order of thermodynamic stability is **10** > **9** > **6i** and it is noteworthy. The dialkylsubstituted maleimides **7a**, **7b**, and **7e** on base catalyzed hydrolysis followed by acidification respectively furnished the natural products 2-carboxymethyl-3-hexylmaleic anhydride (**8a**) (*Aspergillus* FH-X-213),[3q] 2-(β-carboxyethyl)-3-hexylmaleic anhydride (**8b**) (*Pseudomonas cepacica* A-1419),[3g] and the potent ras fernesyl-protein transferase inhibitor chaetomellic acid A (**8e**) (*Chaetomella acutiseta*)[3j] in 85−91% yields. The maleimides **7f** and **7g** on hydrolysis respectively furnished the dibenzylmaleic anhydride **8f** in 97% yield and isopropylbenzylmaleic anhydride **8g** in 94% yield. The formal syntheses of naturally occurring maculalactones A−C (*Kyrtuthrix maculans*)[3d] from dibenzylmaleic anhydride **8f** and nostoclide I (*Peltigera canina*)[3i] from isopropylbenzylmaleic anhydride **8g** are known in the literature.[5h] The analytical and spectral data obtained for natural products **8a**, **8b**, and **8e** and natural product precursors **8f** and **8g** were in complete agreement with the reported data.[5l−n,h] Finally, the maleimides **7c**, **7d**, and **7h** on hydrolysis furnished the expected corresponding unnatural dialkylmaleic anhydrides **8c**, **8d**, and **8h** in 89−97% yields.

SCHEME 1[a]



[a] Reagents and conditions: (i) Et_3N + THF (1:1), reflux, 2 h (98%).

In summary, we have demonstrated a new robust approach to potentially useful natural and unnatural dialkylmaleic anhydrides via the generation of a carbanion on the alkylidenesuccinimide core. We feel that the present general approach to dialkylmaleimides/anhydrides will be useful to design several structurally interesting and biologically important natural and unnatural carbocycles and heterocycles.

Experimental Section

General Procedure for the Synthesis of 2a−c. A solution of *N*-*p*-tolylmaleimide (**1**, 10.00 mmol) and triphenylphosphine (10.00 mmol) in THF (100 mL) was stirred at room temperature for 30 min. To the reaction mixture was added the corresponding aliphatic/aromatic aldehyde (15.00 mmol) and the reaction mixture was refluxed for 10 h. The THF was distilled off in vacuo at 50 °C and the residue was purified by silica gel column chromatography, using a mixture of petroleum ether and ethyl acetate to obtain **2a**-**c** in 89−93% yields.

(*E*)-3-Hexylidene-1-*p*-tolylpyrrolidene-2,5-dione (2a).[7b] White solid (2.47 g, 91%): mp 112−113 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 6 Hz, 3H), 1.22−1.45 (m, 4H), 1.53 (quintet, J = 6 Hz, 2H), 2.23 (q, J = 6 Hz, 2H), 2.37 (s, 3H), 3.37 (d, J = 2 Hz, 2H), 6.93 (tt, J = 8 and 2 Hz, 1H), 7.18 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.7, 20.9, 22.2, 27.5, 29.6, 31.2, 31.8, 125.1, 126.0, 129.2, 129.4, 138.1, 139.6, 168.7, 173.0; MS (*m*/*e*) 271, 242, 228, 214, 200, 189, 172, 133, 107, 95, 81, 67, 53; IR (nujol) ν_{max} 1771, 1749, 1712, 1691, 1676 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.11; H, 7.92; N, 5.07.

Tabulated analytical and spectral data of compounds **2b** and **2c** have been given in the Supporting Information.

General Procedure for the Synthesis of 6a−i. A solution of **2a−c** (1.60 mmol) in THF (20 mL) was added to the slurry of sodium hydride (1.60 mmol) in THF (10 mL) at 0 °C and the reaction mixture was stirred for 30 min. Then, the corresponding alkyl halide (1.60 mmol) was added to the reaction mixture at 0 °C and the solution was stirred for 3 h. The reaction mixture was acidified by 2 N HCl and then it was concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of residue with petroleum ether and ethyl acetate furnished **6a−i** in 65−92% yields.

(*E*)-Ethyl 2-(4-Hexylidene-2,5-dioxo-1-*p*-tolylpyrrolidin-3-yl)acetate (6a). Thick oil (399 mg, 70%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, J = 8 Hz, 3H), 1.21 (t, J = 8 Hz, 3H), 1.27−1.43 (m, 4H), 1.53 (quintet, J = 6 Hz, 2H), 2.29 (q, J = 6 Hz, 2H), 2.39 (s, 3H), 3.01 (dd, J = 17 and 6 Hz, 1H), 3.26 (dd, J = 17 and 4 Hz, 1H), 3.57−3.68 (m, 1H), 4.12 (q, J = 8 Hz, 2H), 6.94 (dt, J = 7 and 2 Hz, 1H), 7.20−7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 14.1, 21.2, 22.4, 28.2, 29.3, 31.5, 34.5, 38.8, 61.2, 126.3, 128.1, 129.5, 129.7, 138.5, 140.6, 169.2, 170.0, 176.1; IR (neat) ν_{max} 1771, 1732, 1713, 1672 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.44; H, 7.80; N, 3.99.

Tabulated analytical and spectral data of compounds **6c−h** have been given in the Supporting Information.

(*E*)-3-Benzylidene-4-(3-methylbut-2-enyl)-1-*p*-tolylpyrrolidine-2,5-dione (6i). Thick oil (468 mg, 85%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.40 (s, 3H), 1.61 (s, 3H), 2.40 (s, 3H), 2.60−2.92 (m, 2H), 4.06 (dt, J = 6 and 2 Hz, 1H), 4.92−5.06 (m, 1H), 7.18 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.40−7.61 (m, 5H), 7.75 (d, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.8, 21.2, 25.9, 27.1, 43.4, 117.1, 126.2, 127.9, 129.0, 129.4, 129.8, 130.0, 130.1, 133.7, 135.4, 136.9, 138.6, 170.2, 176.7; IR (neat) ν_{max} 1769, 1711, 1651 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.08; H, 6.90; N, 4.15.

General Procedure for the Synthesis of 7a−h. To a stirred solution of **6a−h** (0.80 mmol) in THF (10 mL) was added triethylamine (10 mL) and the reaction mixture was refluxed for 48 h and then concentrated in vacuo. The residue was dissolved in ethyl acetate and the organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue with petroleum ether and ethyl acetate furnished **7a−h** in 70−98% yields.

Ethyl 2-(4-Hexyl-2,5-dioxo-1-*p*-tolyl-2,5-dihydro-1*H*-pyrrol-3-yl)acetate (7a). Thick oil (262 mg, 92%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 8 Hz, 3H), 1.29 (t, J = 6 Hz, 3H), 1.20−1.45 (m, 6H), 1.61 (quintet, J = 8 Hz, 2H), 2.38 (s, 3H), 2.50 (t, J = 8 Hz, 2H), 3.52, (s, 2H), 4.21 (q, J = 8 Hz, 2H), 7.15−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 14.0, 21.0, 22.4, 24.2, 28.0, 29.0, 29.2, 31.3, 61.5, 125.6, 129.0, 129.5, 133.0, 137.4, 144.1, 168.5, 169.9, 170.2; IR (neat) ν_{max} 1772, 1740, 1713, 1616 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.63; H, 7.72; N, 4.01.

Tabulated analytical and spectral data of compounds **7b−h** have been given in the Supporting Information.

General Procedure for the Synthesis of 8a−h. To a stirred solution of **7a−h** (0.50 mmol) in a THF−methanol mixture (1:2, 6 mL) was added 20% aqueous KOH solution (4 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated and the residue was acidified with 2 N HCl then extracted with diethyl ether (3 × 20 mL) and the organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue with petroleum ether and ethyl acetate furnished **8a−h** in 85−97% yields.

2-(4-Hexyl-2,5-dioxo-2,5-dihydrofuran-3-yl)acetic Acid (2-Carboxymethyl-3-hexylmaleic anhydride, 8a).[5n] Thick oil (104 mg, 88%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 8 Hz, 3H), 1.15−1.45 (m, 6H), 1.60 (quintet, J = 8 Hz, 2H), 2.50 (t, J = 8 Hz, 2H), 3.57 (s, 2H), 8.60 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 22.4, 24.9, 27.5, 29.1, 31.3, 135.5, 148.1, 165.1, 173.0; IR (Neat) ν_{max} 1820, 1771, 1718, 1216, 925, 670 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.12; H, 6.65.

Tabulated analytical and spectral data of compounds **8b−h** have been given in the Supporting Information.

(*E*)-3-Benzyl-4-(3-methylbut-2-enylidene)-1-*p*-tolylpyrrolidine-2,5-dione (10). This compound was obtained from **6i** by using the procedure used for the synthesis of **7a−h** in 2 h as a thick oil (270 mg, 98%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.99 (s, 3H), 2.01 (s, 3H), 2.35 (s, 3H), 3.22−3.44 (m, 2H), 3.84 (t, J = 4 Hz, 1H), 6.05 (td, J = 12 and 2 Hz, 1H), 6.81 (d, J = 10 Hz, 2H), 7.05−7.32 (m, 7H), 7.56 (dd, J = 14 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.1, 21.2, 27.2, 36.5, 44.5, 120.4, 124.4, 126.3, 127.2, 128.3, 129.2, 129.6, 129.8, 131.6, 135.4, 138.4, 150.2, 169.8, 176.0; IR (Neat) ν_{max} 1765, 1705, 1634 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.06; H, 6.83; N, 4.02.

Acknowledgment. K.P.H. thanks CSIR, New Delhi, for the award of a research fellowship.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **2a**, **2c**, **6a**, **6c**, **6d**, **6f**, **6i**, **7a−d**, **7f−h**, **8a−d**, **8f**, **8h**, and **10** and tabulated analytical and spectral data of compounds **2b**, **2c**, **6c−h**, **7b−h**, and **8b−h**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801284R