An Efficient Synthesis of Dimethylmaleic Anhydride[1]

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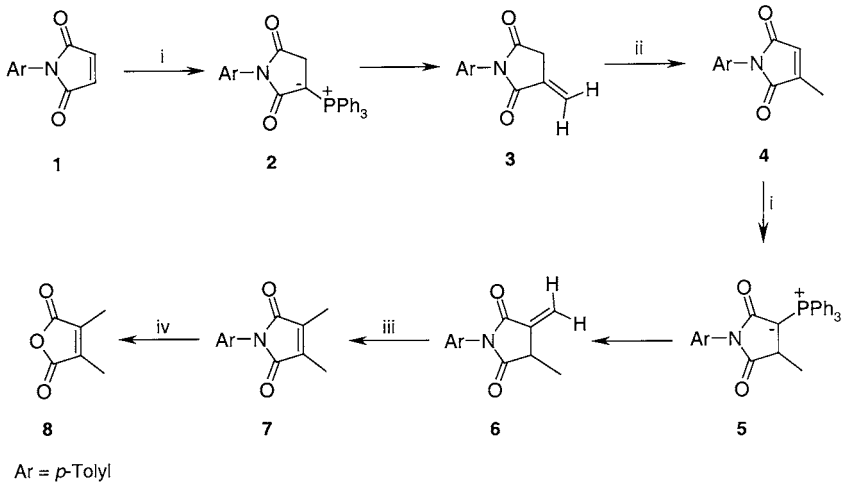
Abstract: A facile three-step synthesis of dimethylmaleic anhydride (**8**) with 74% overall yield has been described starting from maleimide **1**, via methylmaleimide **4**, using two Wittig reactions followed by an alkaline hydrolysis.

Key words: maleic anhydride, maleimide, formaldehyde, condensation, alkylations, Wittig reactions

The utilities of methyl and dimethylmaleic anhydrides/imides have been well-proved in practice.[2,3] Methylmaleic anhydride/imides have been used for the synthesis of bioactive natural products roccellic acid,[4a] tyromycin A,[4b,5c] piliformic acid,[4c] chaetomellic acid A,[4d,5a,b] and pukelimide A.[6] Dimethylmaleic anhydride/imides have been used as a potential building blocks for the synthesis of adriamycin, daunorubicin derivatives,[7] the naturally occuring cyclopentene 1,3-diones,[8] calythrone,[8] chaetomellic acid A[9a] and the 2,3-disubstituted maleic anhydride segment of tautomycin.[9b] Methyl and dimethylmaleic anhydrides/imides have been also used as starting materials for the synthesis of important heterocyclic systems,[10] potential dienophiles in Diels–Alder reactions,[11] and very well-known monomers in polymer chemistry,[12] and some of their derivatives possess herbicidal, fungicidal, insecticidal and defoliant activities.[13,14] As such, the methylmaleic anhydride has been obtained via oxidation of isoprene with 21% yield,[15] cyanohydration of ethyl acetoacetate with 47% overall yield[16] in 4-steps and double dehydrative decarboxylation of citric acid in 2-steps with 34% overall yield.[17] Several synthetic approaches to dimethylmaleic anhydride (**8**) using a variety of strategies are known in the literature.[18] The list of approaches to **8** with 40% plus overall yield includes: (i) oxidation of 2-butene in presence of a metal catalyst with 68% yield;[19] (ii) oxidation of dimethylacetylene in 2-steps with 59% overall yield;[20] (iii) self condensation of ethyl α-bromopropionates with 67% yield;[21] and (iv) an elegant one-pot approach employing 2-aminopyridine with 75% yield.[18c] With our recent success on the synthesis of bioactive natural products,[4,9] we planned to develop a simple and efficient method for the synthesis of alkylmaleimides/anhydrides and symmetrical/unsymmetrical dialkylmaleimides/anhydrides employing the condensation reactions of the maleimide–triphenylphosphine adduct with a series of aldehydes. In this context, we report an easy access to methymaleimide **4**, dimethylmaleimide **7** and dimethylmaleic anhydride (**8**) (Scheme).

The formation of ylide adducts **2** and **5**, respectively, from the reactions of maleimides and methylmaleimides with triphenylphosphine (TPP) in HOAc has been well established.[22] The reaction of maleimide **1** (1 equiv) with TPP (1 equiv) and paraformaldehyde (5 equiv) on refluxing in



Scheme Reagents, conditions and yields: i) TPP, $(CH_2O)_n$, HOAc, reflux, 1 h (92%); ii) TEA, THF, reflux, 3 h (93%); iii) 50 °C, 3 h (98%); iv) a) aq MeOH, KOH, reflux, 2 h, b) H^+/HCl (97%)

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glacial HOAc followed by removal of HOAc *in vacuo* at 70–75 °C and silica-gel column chromatographic purification of the residue yielded the corresponding methylmaleimide **4** in 84% yield, thus offering a new simple method for the synthesis of **4**.[23] The same reactions with 40% aq formaldehyde solution and glyoxalic acid also gave the corresponding imide **4**, but in less yield (30–40%). The methylmaleimide **4** on further reaction with same reagents and reaction conditions furnished the dimethylmaleimide **7** in 91% yield, thus providing a facile approach to **7**.[23] In the two above-mentioned conversions, the formation of ylide adducts **2** and **5**, Wittig reaction and exocyclic to endocyclic double-bond isomerisation takes place in one pot. In the transformation of **1** to **4** it was possible to isolate the corresponding *exo*-isomer **3** with 86% yield by distilling off the HOAc under high vacuum at r.t., as the disubstituted exocyclic to trisubstituted endocyclic double-bond isomerisation process was slow. The conversion of **3** to **4** was accomplished in refluxing THF–Et_3N (1:1) mixture with 93% yield. In the transformation of **4** to **7**, the isolation of corresponding *exo*-isomer **6** in pure form was difficult, as the disubstituted exocyclic to tetrasubstituted endocyclic double-bond isomerisation was relatively very fast. The ^1H NMR spectrum revealed that the isolated product is a mixture of **6** plus **7** in a 7:3 proportion. The complete conversion of **6** to **7** was quantitatively accomplished by heating the neat mixture at 50 °C for 3 h. The conversion of **1** to **7** was also carried out in one pot in a stepwise fashion without the isolation of **4** with 68% yield, while the direct use of two equivalents of TPP results in formation of a phosphorous-containing complex heterocyclic system. The dimethylmaleimide **7** on alkaline hydrolysis in refluxing aq MeOH followed by acidification yielded dimethylmaleic anhydride (**8**) in 97% yield. Several alkylmethyl-substituted maleic anhydrides have been isolated as natural products,[5,9,24] while dimethyl and diethylmaleic anhydrides are the only known[25] symmetrically dialkyl-substituted maleic anhydrides. All our attempts to transform higher analogues of **3** to **4** by using thermal (heat, tetralin reflux), base catalysed (pyridine, TEA, DBU, NaH, *t*-BuOK, *t*-BuLi) and transition metal induced [$RuCl_3$, $HRuCl(PPh_3)_3$, $RhCl_3$, $HRhCl(PPh_3)_3$] trisubstituted exocyclic to trisubstituted endocyclic carbon–carbon double-bond isomerisation met with failure. The studies on synthesis of higher alkyl-substituted maleimides/anhydrides and higher symmetrically/unsymmetrically dialkyl-substituted maleimides/anhydrides are in progress in our laboratories, and we are in search of suitable conditions for the isomerisation of the trisubstitued exocyclic double bond to the trisubstitued endocyclic double bond. The higher analogues of *exo*-isomers **3** and **6** will be potential starting materials for the synthesis of linderanolides.[26]

In summary, we have demonstrated a simple and efficient approach to methyl and dimethyl substituted maleimides/anhydrides.

Melting points are uncorrected. The ^1H NMR spectrums were recorded on Bruker AC 200 NMR spectrometer (200 MHz) with TMS as an internal standard. The mass spectrums were recorded on a Finnigan Mat 1020 mass spectrometer at 70 eV. Column chromatographic separations were done on ACME silica gel (60–120 mesh). Petroleum ether (PE) with a bp range of 60–80 °C was used. Ph_3P, maleic anhydride and paraformaldehyde were obtained from Aldrich Chemical Co. The *N*-*p*-tolylmaleimide (**1**) was obtained in quantitative yield from maleic anhydride via dehydration of corresponding maleanilic acid[4c] [Ac_2O–NaOAc, water bath, 70 °C, 2 h, aq workup].

N-*p*-Tolylmethylenesuccinimide (3)

A mixture of *N*-*p*-tolylmaleimide (**1**, 11.22 g, 60 mmol) and Ph_3P (15.72 g, 60 mmol) in glacial HOAc (150 mL) was stirred at r.t. for 30 min. Paraformaldehyde (9.0 g, 300 mmol) was added to the reaction mixture and it was refluxed for 1 h. HOAc was distilled off *in vacuo* at r.t. and the residue was dissolved in EtOAc (100 mL). The organic layer was washed with H_2O (30 mL), brine (30 mL) and dried (Na_2SO_4). Concentration of the organic layer *in vacuo* followed by column chromatographic purification of the residue (silica gel; PE–EtOAc, 4:1) gave **4**: 102 mg (0.85%) and **3**: 11.04 g (92%); mp 112–114 °C.

IR ($CHCl_3$): 1763, 1702, 1658 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.39 (s, 3 H), 3.51 (t, *J* = 3 Hz, 2 H), 5.74 (t, *J* = 2 Hz, 1 H), 6.47 (t, *J* = 2 Hz, 1 H), 7.20 (d, *J* = 8 Hz, 2 H), 7.30 (d, *J* = 8 Hz, 2 H).

MS: *m*/*z* (%) = 201 (99), 186 (21), 173 (15), 158 (23), 144 (22), 132 (30), 120 (15), 104 (28), 91 (22), 86 (17), 77 (40), 68 (65), 57 (12).

N-*p*-Tolylmethylmaleimide (4)

The imide **4** was prepared using the same procedure as described for the preparation of **3** plus **4**, except that the HOAc was distilled off slowly over a period of 15–20 min at 70–75 °C bath temperature and the oily residue was further heated with stirring for 30 min at the same bath temperature. The residue was dissolved in EtOAc (100 mL) and the organic layer was washed with H_2O (30 mL), brine (30 mL) and dried (Na_2SO_4). Concentration of the organic layer *in vacuo* followed by column purification of the residue (silica gel; PE–EtOAc, 9:1) gave **4**: 10.1 g (84%); mp 115–116 °C.

IR (Nujol): 1710, 1685 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.18 (d, *J* = 2 Hz, 3 H), 2.38 (s, 3 H) 6.47 (q, *J* = 2 Hz, 1 H), 7.20 (d, *J* = 10 Hz, 2 H), 7.27 (d, *J* = 10 Hz, 2 H).

MS: *m*/*z* (%) = 201 (99), 186 (7), 172 (13), 157 (31), 144 (27), 132 (33), 117 (42), 104 (28), 91 (23), 86 (13), 77 (24), 68 (32), 57 (4).

Isomerization of *N*-*p*-Tolylmethylenesuccinimide (3) to *N*-*p*-Tolylmethylmaleimide (4)

To a stirred solution of *N*-*p*-tolylmethylenesuccinimide (**3**, 11.04 g) in THF (70 mL) was added Et_3N (70 mL). The reaction mixture was refluxed for 3 h and then it was concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL) and the organic layer was washed with H_2O (30 mL), brine (30 mL) and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatographic purification of the residue (silica gel; PE–EtOAc, 9:1) gave **4**: 10.24 g (93%).

N-*p*-Tolyl-2-methylene-3-methylsuccinimide (6)

A mixture of *N*-*p*-tolylmethylmaleimide (**4**, 1.005 g, 5 mmol), Ph_3P (1.310 g, 5 mmol) in glacial HOAc (25 mL) was stirred at r.t. for 30 min. Paraformaldehyde (750 mg, 25 mmol) was added and the mixture was refluxed for 30 min. HOAc was distilled off *in vacuo* at r.t., the residue was dissolved in EtOAc (25 mL), and the organic layer

was washed with H_2O (15 mL), brine (15 mL) and dried (Na_2SO_4). Concentration of organic layer *in vacuo* followed by column purification of the residue (silica gel ; PE–EtOAc, 4:1) gave the mixture of dimethylmaleimide **7** and *N*-*p*-tolyl-2-methylene-3-methylsuccinimide (**6**) (**6**:**7** = 7:3): 335 mg (31%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.53 (d, *J* = 8 Hz, 3 H), 2.40 (s, 3 H), 3.47 (m, 1 H), 5.71 (d, *J* = 2 Hz, 1 H), 6.47 (d, *J* = 2 Hz, 1 H), 7.10–7.40 (m, 4 H). (The ^{1}H NMR spectrum of **6** + **7** mixture showed above signals for **6**).

_N_-_p_-Tolyldimethylmaleimide (7)

A mixture of *N*-*p*-tolylmethylmaleimide (**4**, 10.24 g, 50.94 mmol), Ph_3P (13.35 g, 50.94 mmol) in glacial HOAc (150 mL) was stirred at r.t. for 30 min. Paraformaldehyde (7.64 g, 254.7 mmol) was added to the reaction mixture and then it was refluxed for 2 h. HOAc was distilled off slowly over a period of 15 min at 50–60 °C bath temperature and the oily residue was further heated with stirring for 30 min at same bath temperature. Column chromatographic purification of the residue (silica gel; PE–EtOAc, 9:1) gave **7**: 9.90 g (91%); mp 109–110 °C.

IR ($CHCl_3$): 1701, 1507, 1388, 1085 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.06 (s, 6 H), 2.38 (s, 3 H), 7.21 (d, *J* = 8 Hz, 2 H), 7.27 (d, *J* = 8 Hz, 2 H).

MS: *m*/*z* (%) = 215 (99), 200 (6), 186 (8), 172 (13), 156 (46), 144 (13), 132 (23), 117 (14), 104 (20), 91 (16), 77 (17), 65 (8), 54 (17).

Isomerization of _N_-_p_-Tolyl-2-methylene-3-methylsuccinimide (6) to _N_-_p_-Tolyldimethylmaleimide (7)

A mixture of **6** + **7** (100 mg) was heated neat in the oil bath at 50–60 °C for 3 h. The molten thick oily residue was cooled to r.t. to obtain *N*-*p*-tolyldimethylmaleimide (**7**) in quantitative yield. The *exo* compound **6** from **6** + **7** mixture was also completely transformed to **7** at r.t. after 3 days.

_N_-_p_-Tolyldimethylmaleimide (7); One Pot Synthesis

To a stirred solution of maleimide (**1**, 3.74 g, 20 mmol) in HOAc (75 mL) was added Ph_3P (5.24 g, 20 mmol) and the reaction mixture was stirred at r.t. for 15 min. To this mixture was added paraformaldehyde (3 g, 100 mmol) and the reaction mixture was refluxed for 1 h. HOAc was distilled off slowly over 15–20 min at 70–75 °C bath temperature and the oily residue was further heated with stirring for 30 min at same bath temperature. After allowing the reaction mixture to reach r.t., the residue was redissolved in HOAc (75 mL). Ph_3P (5.24 g, 20 mmol) and paraformaldehyde (3 g, 100 mmol) were added to the reaction mixture and it was refluxed for 1 h. The HOAc was distilled off in vacuo at 50–60 °C to obtain a thick oily residue. Column chromatographic purification of the residue (silica gel; PE–EtOAc, 9:1) gave pure **7**: 2.92 g (68% yield).

Dimethylmaleic Anhydride (8)

To the solution of imide (**7**, 9.30 g) in MeOH (100 mL) was added a solution of KOH (12.1 g) in H_2O (25 mL) and the reaction mixture was refluxed for 2 h with stirring. The reaction mixture was concentrated *in vacuo*, the obtained residue was acidified with dilute aq HCl and extracted with EtOAc (3 × 50 mL). The organic layer was washed with H_2O (30 mL), brine (30 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo gave **8**: 5.26 g (97% yield); mp 94–96 °C.

IR ($CHCl_3$): 1748 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.08 (s, 6 H).

MS: *m*/*z* (%) = 126 (67), 82 (99), 67 (5), 54 (22).

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References and Notes

(1) NCL Communication No. 6619.
(2) Gill, B. G.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567.
(3) For references to the use of dimethylmaleic anhydride, see: *Aldrichimica Acta* **1980**, *13*, 53.
(4) (a) Mangaleswaran, S.; Argade, N. P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1764. (b) Mangaleswaran, S.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 5259. (c) Mangaleswaran, S.; Argade, N. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3290. (d) Desai, S. B.; Argade, N. P. *J. Org. Chem.* **1997**, *62*, 4862.
(5) (a) Branchaud, B. P.; Slade, R. M. *Tetrahedron Lett.* **1994**, *35*, 4071. (b) Poigny, S.; Guyot, M.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2175. (c) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 1342.
(6) James, G. D.; Pattenden, G.; Mills, S. D. *Tetrahedron Lett.* **1985**, *26*, 3617.
(7) Baurain, R. Ger. Offen. 2 756 604, **1978**; *Chem. Abstr*. **1979**, *90*, 72437d.
(8) Gedge, D. R.; Pattenden, G. *J. Chem. Soc., Chem commun* **1993**, 2567.
(9) (a) Deshpande, A. M.; Natu, A. A.; Argade, N. P. *J. Org. Chem*. **1998**, *63*, 9557; and references cited therein. (b) Deshpande, A. M.; Natu, A. A.; Argade, N. P. *Synthesis* **2001**, 702.
(10) (a) Argade, N. P.; Balasubramaniyan, V. *Heterocycles* **2000**, *53*, 475. (b) Balasubramaniyan, V.; Argade, N. P. *Tetrahedron* **1989**, *45*, 835.
(11) Kreiser, W.; Janitschke, L.; Ernst, V. L.; Sheldrick, W. S. *Chem. Ber*. **1979**, *112*, 397.
(12) Baumann, M.; Kvita, V.; Roth, M.; Waterhouse, J. S. Swiss Patent 598 253, **1978**; *Chem. Abstr*. **1978**, *89*, 109071n.
(13) Boehner, B.; Baumann, M. Ger. Offen, 2 735 841, **1978**; *Chem. Abstr*. **1978**, *88*, 152415u.
(14) Ciba-Geigy, A.-G. Fr. Demande 2 400 013, **1979**; *Chem. Abstr*. **1980**, *92*, 163836r.
(15) Pichler, H.; Obenaus, F.; Franz, G. *Erdoel, Kohle, Erdgas, Petrochem.* **1967**, *20*, 188.
(16) Kunichika, S.; Oka, S.; Tanaka, K. *Bull. Inst. Chem. Res. Kyoto Univ*. **1966**, *44*, 221.
(17) (a) Shriner, R. L.; Ford, S. G.; Roll, L. J. *Org. Synth. Coll. Vol. 2*; Wiley: Chichester, **1943**, 140. (b) Shriner, R. L.; Ford, S. G.; Roll, L. J. *Org. Synth. Coll. Vol. 2*; Wiley: Chichester, **1943**, 368.
(18) (a) Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rist, G. *Helv. Chim. Acta* **1986**, *69*, 396. (b) Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1984**, *67*, 1897. (c) Baumann, M. E.; Bosshard, H. *Helv. Chim. Acta* **1978**, *61*, 2751; and references cited therein.
(19) Pichler, H.; El, D.; Amin, Z. Ger. Offen. 2 206 713, **1973**; *Chem. Abstr*. **1973,** *79*, 125875b.
(20) Herrera, A.; Hoberg, H. *Synthesis* **1981**, 831; and references cited therein.
(21) Janitschke, L.; Kreiser, W. *Synthesis* **1976**, 314; and references cited therein.
(22) Hedaya, E.; Theodoropulos, S. *Tetrahedron* **1968**, *24*, 2241.

(23) The reaction of TPP-maleic anhydride adduct with aldehydes is known to produce corresponding fulgides while TPP-methylmaleic anhydride adduct does not react with aldehydes.[4d,22]
(24) (a) Sheepeck, J. E.; Liu, W.; Chamberlin, A. R. *J. Org. Chem.* **1997**, *62*, 387. (b) Adeboya, M. O.; Edwards, R. L.; Laessoe, T.; Maitland, D. J.; Whalley, A. J. S. *Liebigs Ann. Chem.* **1996**, 1437. (c) Miyagawa, H.; Hamada, N.; Sato, M.; Ueno, T. *Phytochemistry* **1994**, *36*, 1319.
(25) Froborg, J.; Magnusson, G.; Thoren, S. *J. Org. Chem.* **1975**, *40*, 122.
(26) Seki, K.; Sasaki, T.; Wano, S.; Haga, K.; Kaneko, R. *Phytochemistry* **1995**, *40*, 1175.