Facile Routes to Alkoxymaleimides/Maleic Anhydrides

Manoj Kumar Sahoo, Santosh B. Mhaske, Narshinha P. Argade*

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India
Fax +91(20)5893153; E-mail: argade@dalton.ncl.res.in

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Abstract: New routes to alkoxymaleic anhydrides $1a/b$ have been described in good yields via base-induced chemoselective vinylic substitution of bromo atom in bromomaleimide $4$ with alkanols, and base-induced oxa-Michael addition of alkanols to dialkyl acetylenedicarboxylates $8a/b$ as key steps. An unusual acyl exchange in the conversion of $6a/b$ to $1a/b$ under very simple and mild reaction conditions is noteworthy.

Key words: bromomaleimide, dialkyl acetylenedicarboxylates, oxa-Michael additions, alkoxymaleic anhydrides

A very large number of applications of cyclic anhydrides are known in the literature. Alkoxyl, alkoxylalkyl, alkoxaryl and dialkoxymaleic anhydrides have been used for the synthesis of several bioactive natural products. Methoxymaleic anhydride [3-methoxyfuran-2,5-dione ($1a$)] has been used for the synthesis of bioactive natural products narthigenine, penicillic acid, and lucidone. Highly regioselective Wittig reactions and metal hydride reductions have been performed on $1a$ to obtain precursors of bioactive natural products, the butyro lactones. The anhydride $1a$ has been also used for the synthesis of benzothiazolylacrylic acid. The corresponding methoxymaleimide has been used by Pattenden et al. for the synthesis of a constituent of the marine blue-green algae pukeleimide A. To date two syntheses of methoxymaleic anhydride ($1a$) are known. The first synthesis involves diazomethane-induced methylolation of the enol of ethyl oxaloacetate as a key step. The second synthesis has been completed by using diazomethane for methylolation of the pyridine salt of hydroxymaleic anhydrides, which was obtained from tartaric acid in two steps. Both the above synthesis of $1a$ use poisonous and explosive diazomethane for methylolation reactions. Development of new, simple, general, and efficient routes to these potential building blocks, the cyclic anhydrides is a challenging task of current interest. Very recently we have completed a rapid access to alkoxysuccinic acids via oxa-Michael addition of alcohols to alkyl maleanilates, and in continuation of our ongoing programme on the synthesis of several natural and unnatural cyclic anhydrides, we report herein reasoned and planned new routes to $1a/b$, using alkanols as a source of OR group (Scheme 1).

Scheme 1 Reagents and conditions: (i) Br$_2$, CCl$_4$, reflux, 1 h (98%); (ii) TEA, THF, 0 °C, 2 h (98%); (iii) Et$_3$N, ROH, reflux, 1 h (70–75%); (iv) (a) aq KOH, MeOH, r.t., 1 h, (b) H$^+$/HCl (96%); (v) Ac$_2$O–HOAc (1:1), 80 °C, 4 h (95%); (vi) Et$_3$N, ROH, r.t., 2 h (94–96%); (vii) (a) aq KOH, MeOH, r.t., 6 h, (b) H$^+$/HCl (93–96%); (viii) SOCl$_2$, reflux, 24 h (64–65%).
The reaction of N-phenylmaleimide (2) with bromine in refluxing CCl₄ gave the trans-dibromosuccinimide 3 in quantitative yield. Triethylamine-induced dehydrobromination of 3 at 0 °C yielded the bromomaleimide 4 in nearly 98% yield. The chemoselective base-catalyzed vi-
nylic substitution of bromine in imide 4 with meth-
anol/ethanol gave the alkoxymaleimides 5a/b in 70–75% yields. The reaction of dibromosuccinimide 3 with Et₃N–
MeOH also gave 5a, but in 20–25% yield only. In our hands the compounds 5a/b on acid-catalyzed hydrolysis (HCl, reflux, 1 h) underwent dealkylation reactions and furnished only decomposed/polymeric gums. The base-
induced regioselective hydrolysis of 5a/b at room tempera-
ture gave the corresponding maleanilic acids 6a/b in quantitative yields. The cleavage of amide bond in anilic acids generally demands strong reaction conditions. Remarkably the maleanilic acids 6a/b in 1:1 mixture of acetic anhydride and acetic acid at 80 °C underwent a smooth acyl exchange reaction and furnished the mixture of aceto-
anilide and desired alkoxymaleic anhydrides 1a/b in 95% yield. We feel that, the present observed acyl exchange re-
action is substrate, reagent and reaction conditions specif-
ic. The free carboxylic group, carbon–carbon double bond with cis geometry and acetic anhydride/acetic acid combi-
nation is necessary for the above acyl exchange reaction. We also feel that the present exchange reaction is plausi-
bly taking place via the intermediate acyclic imides 7a/b.

In our second approach we studied the base-induced oxa-
Michael addition of alcohols to 8a/b to obtain exclusively or in major amounts, the E-isomers of the dialkyl alkox-
nylates 9a/b. All our attempts using different temperatures and bases met with failure and we always got the 10a/b as major products. The best yield of 9a/b plus 10a/b (94–96%) was obtained from the reaction of 8a/b and alkanols using triethylamine as a base at room tempera-
ture in 2 hours (9a:10a = 30:70 and 9b:10b = 20:80, by ¹H NMR spectroscopy). We could very easily separate these E- and Z-isomers 9a/b and 10a/b by silica gel col-
mum chromatography for characterization. Potassium hy-
droxide-catalyzed hydrolysis of E- and Z-mixture of ester 9a/b and 10a/b followed by acidification gave the corres-
ponding mixture of acids 11a/b and 12a/b in 93–96% yields with same E/Z ratio. The pure esters 9a/b and 10a/
b were also similarly hydrolyzed to corresponding acids 11a/b and 12a/b respectively. The mixture of acids 11a plus 12a and 11b plus 12b in refluxing thionyl chloride re-
spectively furnished the desired alkoxymaleic anhydrides 1a and 1b in 64–65% yield. Both isomerization of Z-
isomers 12a/b to E-isomers 11a/b and dehydrative ring-clo-
ture took place in one-pot. The analytical and spectral data obtained for 1a/b were in complete agreement with reported data. The overall yield of 1a/b in five steps (2 to 1a/b) and three steps (8a/b to 1a/b) were 61–66% and 56–60% respectively. The one-step conversion of meth-
oxamaleic anhydride (1a) to bioactive natural products nathrigenine (antibiotic) and penicillic acid (antimicrob-
ial, antitumor, blood vessels dilation, antiiduetic) are known.

In summary, we have demonstrated new general ap-
proaches to alkoxymaleic anhydrides via base induced vi-
nylic substitution of bromo atom in 4 with alkanols and oxa-Michael addition of alkanols to dialkyl acetylenedicarboylates 8a/b. Such a chemoselective nucleophilic vi-
nylic substitutions under very simple and mild reaction conditions will be useful in organic synthesis. The ob-
served substrate, reagent and reaction conditions specific for an unusual acyl exchange reaction is noteworthy.

Melting points are uncorrected. ¹H NMR spectra were recorded on Bruker AC 200 NMR spectrometer (200 MHz) with TMS as an internal standard. Mass spectra were recorded on Finnigan Mat 1020 mass spectrometer at 70 eV. Column chromatographic separations were done on ACME silica gel (60–120 mesh). Petroleum ether with a bp range of 60–80 °C was used. Dimethyl acetylenedicarbo-
ylate and diethyl acetylenedicarboxylate were obtained from Ald-
rich Chemical Co. N-Phenylmaleimide (2) was prepared in quantitative yield using known procedure.

trans-2,3-Dibromo-N-phenylsuccinimide (3)

To a solution of N-phenylmaleimide (2; 1.73 g, 10 mmol) in CCl₄ (15 mL) was added dropwise a solution of Br₂ (0.57 mL, 11 mmol) in CCl₄ (10 mL) at r.t. After complete addition, the reaction mixture was refluxed for 1 h, and then allowed to cool to r.t. The precipitate was filtered and washed with CCl₄ (2 × 5 mL) and dried; yield: 3.26 g (98%); mp 155–157 °C.

IR (Nujol): 1798, 1728, 1591 cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ = 4.87 (s, 2 H), 7.30–7.70 (m, 5 H).

¹C NMR (CDCl₃, 50 MHz): δ = 41.9, 44.4, 126.0, 129.4, 130.8, 130.9, 169.2, 169.5.

MS: m/z = 335, 333, 331, 253, 251, 196, 173, 144, 128, 119, 104, 91, 77.

Anal. Calcd for C₁₀H₇Br₂NO₂: C, 36.07; H, 2.12; N, 4.21. Found: C, 35.88; H, 2.19; N, 4.35.

2-Bromo-N-phenylmaleimide (4)

To a solution of 3 (3.0 g, 9 mmol) in THF (30 mL) was added drop-
wise a solution of Et₃N (1.38 mL, 9.9 mmol) in THF (5 mL) at 0 °C and the mixture was stirred for 2 h. The mixture was allowed to warm to r.t. and concentrated in vacuo. The residue was dissolved in EtOAc and washed with H₂O, brine and dried (Na₂SO₄). Concentration of the organic layer in vacuo furnished 4; yield: 2.23 g (98%); mp 161–163 °C.

IR (Nujol): 1782, 1716, 1713, 1599 cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ = 7.03 (s, 1 H), 7.30–7.70 (m, 5 H).

¹C NMR (CDCl₃, 50 MHz): δ = 126.0, 128.2, 129.1, 131.0, 131.7, 131.8, 164.1, 167.3.

MS: m/z = 253, 251, 211, 196, 171, 144, 128, 119, 104, 91, 77, 64.

Anal. Calcd for C₁₀H₇BrNO₂: C, 47.65; H, 2.40; N, 5.56. Found: C, 47.71; H, 2.29; N, 5.50.

2-Methoxy-N-phenylmaleimide (5a)

To a solution of 4 (1.0 g, 3.97 mmol) in MeOH (10 mL) was added a solution of Et₃N (0.61 mL, 4.37 mmol) in MeOH (5 mL) and the reaction mixture was refluxed for 1 h. Concentration of the mixture in vacuo followed by silica gel column chromatographic purifi-
cation of the residue using petroleum ether–EtOAc (8:2) as eluent gave 5a: yield: 604 mg (75%); mp 99–101 °C.

IR (Nujol): 1778, 1730, 1715, 1643, 1599 cm⁻¹.
Anal. Calcd for C12H13NO4: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.20; H, 5.69; N, 6.03.

1H NMR (CDCl3, 200 MHz): δ = 4.02 (s, 3 H), 5.58 (s, 1 H), 7.25–7.55 (m, 5 H).

13C NMR (CDCl3, 50 MHz): δ = 58.9, 96.3, 125.9, 127.6, 128.9, 131.0, 160.6, 164.2, 168.8. MS: m/z = 203, 174, 147, 119, 105, 88, 84, 77, 69, 64, 59.

Anal. Calcd for C6H5NO3: C, 66.47; H, 5.02; N, 6.53. Found: C, 66.57; H, 5.02; N, 6.53.

2-Ethoxymaleanilic Acid (6b)

To a solution of 5a (500 mg, 2.46 mmol) in MeOH (5 mL) was added dropwise Et3N (2.7 mL, 19.37 mmol) and the reaction mixture was stirred at r.t. for 2 h. Concentration of the mixture in vacuo followed by column chromatography using petroleum ether–EtOAc (9:1) as eluent gave 6b in a total yield of 96%.

1H NMR (CDCl3, 200 MHz): δ = 1.33 (t, J = 6 Hz, 3 H), 3.69 (s, 1 H), 7.10 (t, J = 6 Hz, 1 H), 7.31 (t, J = 8 Hz, 2 H), 7.57 (d, J = 8 Hz, 2 H).

Anal. Calcd for C10H16O5: C, 55.54; H, 7.46; Found: C, 55.41; H, 7.49.

10a

Yield: 4.17 g (68%); thick oil.

IR (CHCl3): 1745, 1726, 1641, 1437, 1362, 1269 cm⁻¹.

1H NMR (CDCl3, 200 MHz): δ = 3.75 (s, 3 H), 3.84 (s, 3 H), 3.93 (s, 3 H), 6.18 (s, 1 H).

13C NMR (CDCl3, 50 MHz): δ = 51.1, 52.4, 56.6, 92.7, 162.1, 163.5, 165.8.


Method 2-Methoxymaleimide acid (6a): 300 mg. 1.36 mmol) was heated at 80 °C in a mixture of HOAc and Ac₂O (1:1, 10 mL) for 4 h. Ac₂O and HOAc were distilled off in vacuo and the residue was purified by silica gel column chromatography using petroleum ether–EtOAc (8:2) as eluent to obtain 1a (165 mg, 95%); mp 152–153 °C.

Method B: 2-Methoxymaleimide acid (6a): 300 mg, 1.36 mmol) was heated at 80 °C in a mixture of HOAc and Ac₂O (1:1, 10 mL) for 4 h. Ac₂O and HOAc were distilled off in vacuo and the residue was purified by silica gel column chromatography using petroleum ether–EtOAc (8:2) as eluent to obtain 1a (165 mg, 95%); mp 152–153 °C.

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References

(1) NCL Communication No. 6633.
(14) Mhaske, S. B.; Argade, N. P., unpublished results.