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# An expeditious synthesis of natural and unnatural disubstituted maleic anhydrides

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**Abstract**—A facile entry to the synthesis of natural and unnatural substituted maleic anhydrides based on the Barton radical decarboxylation is described. The radicals, generated by the photolysis of *N*-hydroxy-2-thiopyridone esters derived from succinic and alkyl acids reacted, respectively, with electron deficient olefin phenyl maleimide by a consecutive two-step radical addition, afforded the corresponding disubstituted maleic anhydrides **1a**–**f**.


A number of natural products containing a substituted maleic anhydride unit have been reported in the literature.[1] They exhibit a range of biological activities, including antibacterial activity,[2] immunomodulating,[3] and plant growth promoting.[4] Among them the unnamed dialkylsubstituted maleic anhydrides **1a** and **1b** were isolated from the soil, *Pseudomonas cepacia* A-1419 by Soda and co-workers,[5] while **1c** was prepared chemically by the dehydration of natural spiculisporic acid.[6] Anhydride **2** and cordyanhydride A **3** have recently been isolated as bioactive fungal natural products[7,8] (Fig. 1).

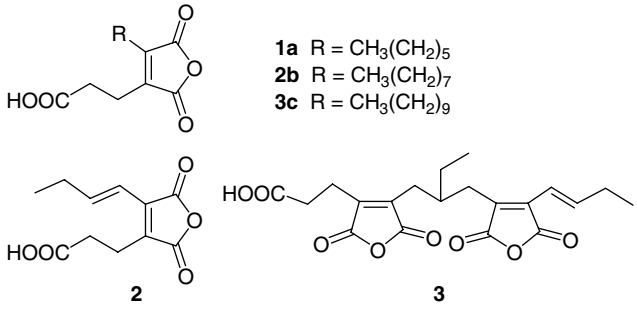


**Figure 1.**

Two approaches for the synthesis of dialkylsubstituted maleic anhydrides **1a**–**b** based on ionic chemistry were reported in the literature: copper mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate[9] and chemoselective $S_N2/S_N2'$ coupling of Grignard reagents.[10]

We reported previously that the carbon–carbon bond formation using free radical reactions might be the most suitable way to synthesize branched-chain maleic anhydride.[11] In this respect the Barton decarboxylation reaction using thiohydroxamic esters as a source of carbon radicals, seemed the method of choice.[12] In this letter, we report a further extension of this reaction towards the total synthesis of anhydrides **1a**–**c** and some analogues using a double radical decarboxylation.

Our strategy for the synthesis of **1** is based on a two-step radical addition to phenyl maleimide. In the first step, the readily available succinic acid monomethyl ester **4** was converted into its thiohydroxamic ester **5**, by the DCC coupling method in the presence of 1-hydroxypyridine-2(1*H*)-thione. Irradiation in situ with a tungsten light (500 W) of **5**, in the presence of phenyl maleimide (5 equiv), gave the intermediate addition product **6** in 82% yield. The oxidation of **6** with *m*-CPBA, followed by the elimination of the resulting sulfoxide produced an unsaturated **7** in 90% yield. The *syn* elimination of

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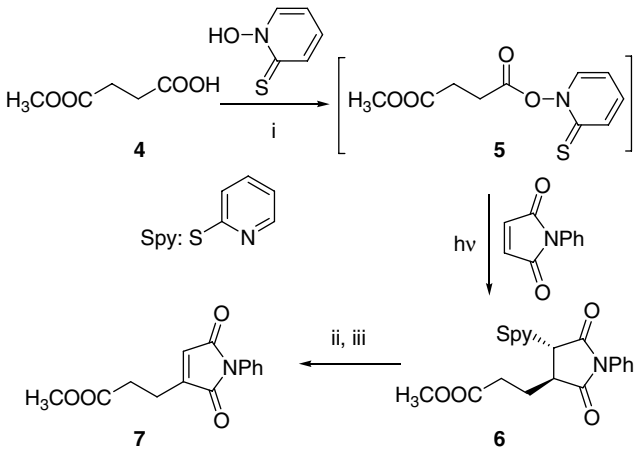
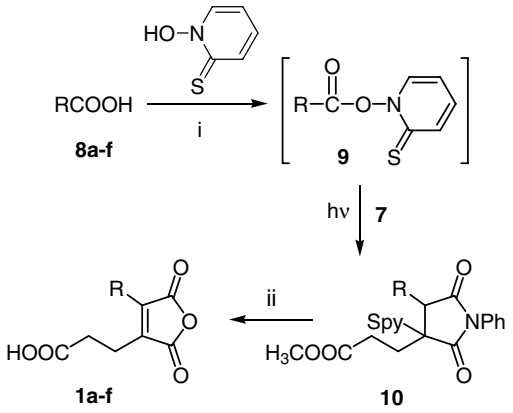



**Scheme 1.** Reagents and conditions: (i) DCC, $CH_2Cl_2$, rt, 2 h, then phenyl maleimide (5 equiv) h$\nu$, 15 °C, 30 min (82%); (ii) *m*-CPBA, $CH_2Cl_2$, 0 °C, 1 h; (iii) toluene, 110 °C, 1 h, (90% from **6**).

the 2-pyridylthio group of the intermediate **6** established the trans stereochemical relationship of the 2-pyridylthio group and the alkyl substituents, which is the result of a trans addition of the radical to phenyl maleimide (Scheme 1).[13]

Having compound **7** in hand, it was subjected as the olefin trap to a second step radical reaction. Thus acid **8** was converted to its thiohydroxamic ester **9** as was described for **5**, and irradiation in situ with tungsten light (500 W) in the presence of olefin **7** (5 equiv), produced the intermediate addition product **10** as a mixture of isomers,[14] which was further treated with KOH in MeOH–THF to furnish the desired dialkylsubstituted maleic anhydride **1**[15] as the sole isomer (Scheme 2). The natural and unnatural anhydrides **1a–f** were obtained in the range of 42–48% yield over two steps from acids **8a–f**. Oleic acid **8f** was successfully decarboxylated in the presence of olefin **7** without intramolecular addition to the double bond to give the disubstituted anhydride **1f**. The results are summarized in Table 1.




**a**: R = $CH_3(CH_2)_5$ **d**: R = $CH_3(CH_2)_8$
**b**: R = $CH_3(CH_2)_7$ **e**: R = $CH_3(CH_2)_{10}$
**c**: R = $CH_3(CH_2)_9$ **f**: R = $(Z)CH_3(CH_2)_7CH{=}CH(CH_2)_7$

**Scheme 2.** Reagents and conditions: (i) DCC, $CH_2Cl_2$, rt, 2 h, then 5 equiv of **7**, h$\nu$, 15 °C, 30 min; (ii) KOH, THF–MeOH, reflux, 3 h.

**Table 1.**

| Entry | Acid | % Product (yield) |
|---|---|---|
| 1 | **8a** | **1a** (42) |
| 2 | **8b** | **1b** (42) |
| 3 | **8c** | **1c** (43) |
| 4 | **8d** | **1d** (46) |
| 5 | **8e** | **1e** (48) |
| 6 | **8f** | **1f** (45) |

In summary, we have described an efficient and concise synthesis of anhydride **1**. The facile synthesis and exceptionally mild conditions of the reaction described herein offer a rapid synthetic access to other analogues bearing suitable functionalities on the alkyl side chain, and will allow further biological evaluation.

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13. For more detail of trans addition of radical to maleic anhydride see: (a) Branchaud, B. P.; Slade, R. M. *Tetrahedron Lett.* **1994**, *35*, 4071; (b) Barton, D. H. R.; Gateau-Olesker, A.; Gero, S. D.; Lacher, B.; Tachdjian, C.; Zard, S. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1790.
14. After irradiation, the reaction mixture was subjected to column chromatography over silica gel. The excess of olefin **7** was recovered along with compound **10**, which was used immediately in the next step without further characterization. So the stereochemical relationships trans and *syn* of the 2-pyridylthio group and the alkyl substituent of compound **10** were not determined. For more detail on the stereochemistry of radical addition to monosubstituted maleic anhydride see: Giese, B.; Damm, W.; Witzel, H.; Zeitz, H. G. *Tetrahedron Lett.* **1993**, *34*, 7053.
15. *General procedure for synthesis of disubstituted maleic anhydrides* **1**. To a solution of acid **8** (1 mmol) and 1-hydroxypyridine-2(1*H*)-thione (147 mg, 1.2 mmol) in dry $CH_2Cl_2$ (10 mL) was added DCC (248 mg, 1.2 mmol) under argon. The mixture was stirred at room temperature for 2 h. Olefin **7** (1.296 g, 5 mmol) was then added, and the mixture irradiated with a tungsten lamp (500 W) at 10–15 °C for 30 min. The solution was filtered to remove the urea and the filtrate was washed with saturated $NaHCO_3$, water, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified over silica gel using cyclohexane–EtOAc (80:20) as eluent to give compound **10**, which was used in the next step without further characterization. To a solution of imide **10** in THF–MeOH (6 mL, 1:2) was added a solution of KOH (0.6 g) in water (2 mL), and the reaction mixture was refluxed for 3 h with stirring. The solvent mixture was removed under reduced pressure, and the residue was dissolved in water, and extracted with ether. The aqueous phase layer was acidified with diluted HCl and extracted with ether. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel using cyclohexane–EtOAc as an eluent to yield compound **1**.
Spectral data of compounds **1a**, **1b**, and **1c** are in agreement with the reported literature.[5,6]
*3-(4-Nonyl-2,5-dioxo-2,5-dihydrofuran-3-yl)propanoic acid* (**1d**). Oil; IR (neat) 2917, 2850, 1768, 1712, 1257, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz), $\delta$ 2.76 (s, 4H), 2.49 (t, $J = 7$ Hz, 2H), 1.58 (m, 2H), 1.28 (m, 12H), 0.88 (t, $J = 6.5$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 62.5 MHz), $\delta$ 176.2, 165.4, 165.2, 146.1, 141.2, 31.6, 30.8, 29.5, 29.4, 29.2, 29.0, 27.7, 24.4, 22.4, 19.4, 13.9; Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84, H, 8.16. Found: C, 64.65, H, 8.30.
*3-(4-Undecyl-2,5-dioxo-2,5-dihydrofuran-3-yl)propanoic acid* (**1e**). Mp 54–55 °C; IR (KBr) 2917, 2850, 1768, 1712, 1257, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz), $\delta$: 2.76 (s, 4H), 2.49 (t, $J = 7$ Hz, 2H), 1.58 (m, 2H), 1.28 (m, 16H), 0.88 (t, $J = 6.5$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 62.5 MHz), $\delta$ 177.1, 165.6, 165.4, 146.3, 141.4, 31.9, 30.9, 29.6, 29.5, 29.4, 29.32, 29.28, 29.2, 27.9, 24.6, 22.7, 19.6, 14.1; HRMS *m*/*z*: calcd for $C_{18}H_{29}O_5$ [MH] 325.2015, found 325.2022.
*(Z)-3-(4-(Heptadec-8-enyl)-2,5-dioxo-2,5-dihydrofuran-3-yl)propanoic acid* (**1f**). Oil; IR (neat) 2927, 2856, 1768, 1714, 1274, 912 $cm^{-1}$; $^1H$ NMR($CDCl_3$, 250 MHz), $\delta$: 5.35 (m, 2H), 2.77 (s, 4H), 2.50 (t, $J = 7$ Hz, 2H), 2.01 (m, 4H), 1.57 (m, 2H), 1.26 (m, 20H), 0.88 (t, $J = 6.5$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 62.5 MHz), $\delta$: 176.4, 165.6, 165.4, 146.3, 141.4, 130.1, 129.6, 31.9, 30.9, 30.3, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 29.0, 27.9, 27.2, 27.1, 24.6, 22.7, 19.6, 14.1; HRMS *m*/*z*: calcd for $C_{24}H_{39}O_5$ [MH] 407.2797, found 407.2851.