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A facile synthesis of alkyl substituted maleic anhydrides: radical approach

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ABSTRACT

Synthetic background for the preparation of alkyl substituted maleic anhydrides and maleimides based on radical alkylation of 2,3-dichloromaleic anhydride (maleimide) by hydrocarbons was developed. The best conditions for the selective synthesis of 2-alkyl-3-chloro- and unsymmetrically substituted dialkylmaleic anhydrides were elaborated.

1. Introduction

Maleic anhydrides and maleimides are essential intermediates for the synthesis of fine chemicals, including natural substances and their analogues.[1] In addition, a number of natural products containing a substituted maleic anhydride unit have been reported in the literature. They are of great interest due to antibacterial, plant growth promoting, immunomodulating activities, and also activity against Lewis lung carcinoma cell lines.[2]

There are several synthetic approaches for the synthesis of alkyl- and dialkylsubstituted maleic anhydrides reported in the literature.[3] On the one hand, ionic chemistry-based synthetic routes generally employ either different organometallic coupling (S_N2/S_N2' coupling of Grignard reagents,[4] Negishi or Suzuki coupling[5]) or copper-mediated tandem vicinal difunctionalization of dimethyl acetylenedicarboxylate.[6]

On the other hand, the target products can be generated in metal-free radical approaches. Firstly, synthesis of substituted maleimides, based on the Barton decarboxylation reaction,[7] should be mentioned. The key phase of the latter method is the three-step functionalization of maleimide (Scheme 1). Radical addition of the thiohydroxamic ester of the appropriate acid **1** gives addition product **2**, and subsequent oxidation of the intermediate, followed by the decomposition of the corresponding sulfone, produces substituted maleimide **3**.

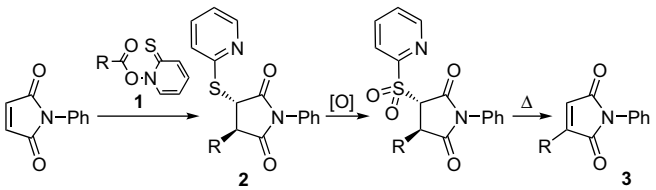
Another intriguing radical approach is a not yet sufficiently developed one-step radical chain addition–elimination reaction with 2,3-dichloromaleic anhydride **4** (Scheme 2).[8]

Taking advantage of the knowledge of 2,3-dichloromaleic anhydride alkylation kinetics,[9] we developed selective, cost-effective and time-efficient preparative methods for substituted maleic anhydrides' synthesis. Synthetic results are summarized in Table 1.

2. Discussion

For our studies we addressed cyclohexane, toluene and 1,4-dioxane as representative examples of different types of 'hydrocarbons', producing correspondingly alkyl, benzylic, and α-alkoxyalkyl radicals. It was found that the rate of the reaction greatly depends on the nature of the 'hydrocarbon' and decreases in the row: alkyl>benzyl>1,4-dioxan-2-yl. We also determined that the rate of substitution of the first chlorine atom is about 30–100 times greater than the rate of the second substitution in **4**. This observation provided us with a background for selective synthesis of 2-alkyl-3-chloromaleic and 2,3-dialkylmaleic anhydrides, and consequently products **6**–**9** were isolated in good yields (60–80%). The reaction with 1,4-dioxane proceeds slowly and some polymerization of the product occurs, therefore **10** was obtained in only 40% yield, and all attempts to obtain 3,4-di-(1,4-dioxan-2-yl) maleic anhydride were unsuccessful.

Owing to the high selectivity of the substitution of the two chlorine atoms in **4**, a one-pot synthesis of unsymmetrically dialkylsubstituted maleic anhydrides seemed feasible. Thus, anhydride **11** was synthesized in 50% yield starting from 2,3-dichloromaleic anhydride. When we attempted to obtain 2-benzyl-3-cyclohexylmaleic anhydride **20**, to our surprise, we observed that the substitution of the alkyl radical competes with the substitution of the second chlorine atom (Scheme 3). In this case, a mixture of products was obtained.



Scheme 1. Synthesis of substituted maleimides based on Barton decarboxylation.

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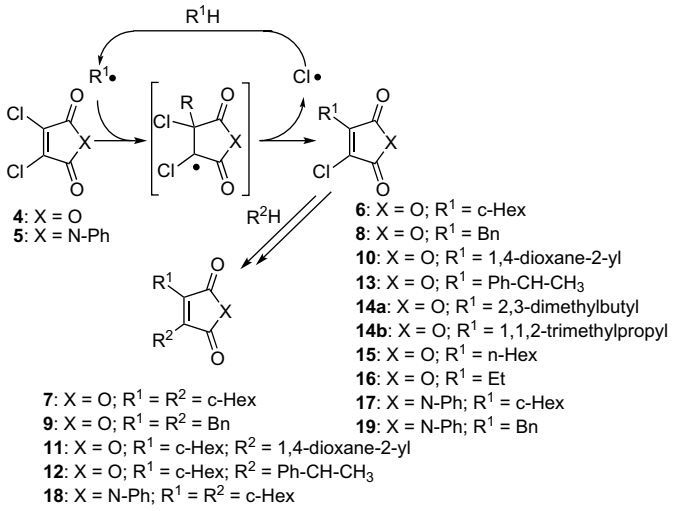
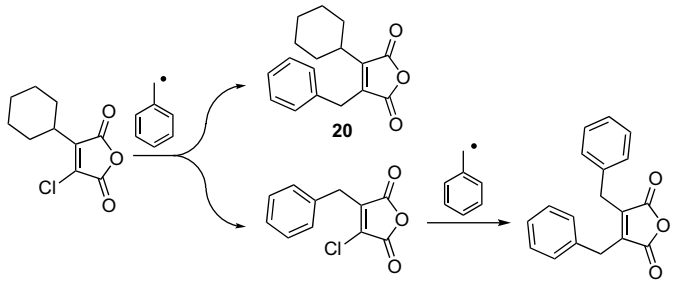


Scheme 2. Synthesis of substituted maleic anhydrides based on radical addition–elimination reaction.

At this point a discrepancy with previous synthesis was raised. There was no side alkyl–alkyl substitution in the preparation of **11**. Therefore, we believe that the steric factor plays a general role in the alkyl radical exchange. To support this hypothesis, we have assumed that the reaction of **6** with more bulky ethylbenzene should proceed without exchange of cyclohexyl substituent, and, indeed, this reaction led to **12** without any side process.

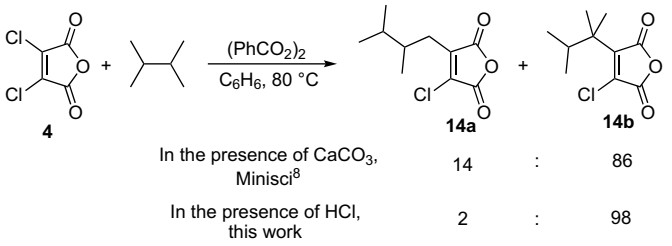
In the chain process of alkylation of 2,3-dichloromaleic anhydride, abstraction of a hydrogen atom from the hydrocarbon proceeds by the chlorine radical. Thus, there is a question of regioselectivity in the case of hydrocarbons with non-equivalent C–H bonds. Some solvents, such as benzene or carbon disulfide, are known to give complexes with a chlorine atom, thus increasing the selectivity of hydrogen abstraction process.[10] Since ethylbenzene is



Scheme 3. Alkyl exchange in radical benzylation of 2-chloro-3-cyclohexylmaleic anhydride.

such a solvent, the reaction of **4** in neat ethylbenzene selectively leads to **13** (quantity of β-isomer is less than 0.1%). However, reaction of **4** in neat 2,3-dimethylbutane results in a mixture of isomers. In our previous kinetic investigations,[9] we found that the reaction regioselectivity is increased with increasing HCl concentration in the reaction medium. Using this fact together with a complexing solvent strategy we improved the reaction selectivity of **4** with 2,3-dimethylbutane up to 2:98 (**14b**/**14a**) (Scheme 4).

We can assert that solvent and HCl effects are powerful instruments to generate selectively the most thermodynamically stable alkyl radical and subsequent alkylation product, but selective



Scheme 4. Reaction of 2,3-dichloromaleic anhydride with 2,3-dimethylbutane.

Table 1
Synthesis of substituted maleic anhydrides

Substrate	Reagent	Product	Method[a]	Yield, %	Properties	Literature yield, % (time, h)
4	Cyclohexane	**6**	A 5%[b] $(PhCO_2)_2$, reflux, 40 min	80	Bp 132–135 °C (2 Torr)	72 (3)[8c] 91 (20)[8b]
4	Cyclohexane	**7**	A 2[c]×[20% $(PhCO_2)_2$, reflux, 3 h]	70	Mp 117–119 °C (from cyclohexane)	76 (100)[8b]
4	Toluene	**8**	A 10% (t-BuO)$_2$, reflux, 2 h	63	Mp 54–55 °C (from hexane)	48 (2)[8c] 47 (54)[8b]
4	Toluene	**9**	A 5×[10% (t-BuO)$_2$, reflux, 2 h]	58	Oil	18 (7 steps)[1b]
4	1,4-Dioxane	**10**	A 3×[5% $(PhCO_2)_2$, 85 °C, 2 h]	40	Mp 98–99 °C (from Et_2O)	35 (3)[8c] 20 (80)[8b]
4	Cyclohexane 1,4-Dioxane	**11**	D	52	Oil	—
6	Ethylbenzene	**12**	A 5×[15% (t-BuO)$_2$, reflux, 2 h]	32	Oil	—
4	Ethylbenzene	**13**	A 20% $(PhCO_2)_2$, 90 °C, 2 h	20	Mp 52–54 °C (from hexane)	—
4	2,3-Dimethylbutane	**14b**	B	78	Oil	15 (2)[8c] (**14a**/**14b**=86:14)
4	n-Hex$SO_2CH_2CH{=}CH_2$	**15**	C	35	Oil	—
4	Et$SO_2CH_2CH{=}CH_2$	**16**	C	33	Oil	—
5	Cyclohexane	**17**	A 10% $(PhCO_2)_2$, reflux, 3 h	70	Mp 89–91 °C (from cyclohexane)	—
5	Cyclohexane	**18**	A 4×[10% $(PhCO_2)_2$, reflux, 3 h]	30	Oil	—
5	Toluene	**19**	A 2×[10% (t-BuO)$_2$, reflux, 2.5 h]	52	Mp 105–107 °C (from hexane)	—

[a] See Section 3.
[b] mol % according to substrate.
[c] Number of repetitions.