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Antimony pentachloride catalyzed Diels-Alder reactions: improved regioselectivity in the synthesis of dialkyl naphthoquinones

Ruth Leandro Nunes and Lothar Wilhelm Bieber*

Departamento de Química Fundamental, Universidade Federal de Pernambuco, Recife 50740-540, Brazil

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Abstract—Improved regioselectivity in catalyzed Diels–Alder (DA) cycloadditions between non-symmetrical benzoquinones and mono-substituted butadienes is achieved by use of $SbCl_5$. After oxidation, good yields of dialkylnaphthoquinones are obtained. The greater steric demand in comparison to other Lewis acids (LAs) seems to favor the less hindered transition state. © 2000 Elsevier Science Ltd. All rights reserved.

1,4-Benzoquinones are important dienophiles for the construction of polycyclic natural products. However, when non-symmetrically substituted reactants are used, low selectivity is often observed and the separation of the isomers can be problematic. For example, the thermal reaction of toluquinone 1a and piperylene 2a (Scheme 1) produces, after oxidative work up, a mixture of the naphthoquinones in a ratio of 3a:4a of 30:70.1 BF₃ catalysis inverts the isomer ratio 3a:4a to 69:31, but obtaining pure **3a** by crystallization or chromatography is extremely difficult and low yielding.² 2,5-Dimethyl-1,4naphthoquinone, 3a, was the starting material in our synthesis of Mansonone F recently described.³ Although **3a** can also be obtained by the oxidation of 1,5-dimethylnaphthalene, the high cost of the latter and the low yield of the reaction prompted us to reexamine the alternative Diels-Alder (DA) reaction.

The improved selectivity obtained by BF₃ catalysis was rationalized in terms of Frontier Molecular Orbital Theory.² The uncatalyzed reaction favors the regioisomer 4a, due to electronic effects. When BF₃ is used, it complexes preferentially, not exclusively, on carbonyl-4 of 1a, leading to inverted electronic distribution, favoring regioisomer 3a. Such preference is not yet completely understood, but it is possible to explain it based on steric interactions between the Lewis acid (LA) and the methyl group of 1a, since the basicity of the carbonyl groups should be quite similar. Consequently, it can be expected that a larger LA could still improve the selectivity. Amongst the simple, commercially available LAs commonly used in synthesis, SbCl₅ is probably the bulkiest because of the high atomic radius and coordination number of Sb. To our surprise, its use in DA reactions described in the literature is restricted to LA



Scheme 1.

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^{*} Corresponding author. Fax: (55) 81 271-8442; e-mail: lothar.bieber@dqfex.ufpe.br

strength studies and, together with others acids, as a comparison standard for zeolite catalysts.^{4,5}

Variable conditions of temperature, solvent, concentration and ratio of reagents were tested. The best results were achieved when a solution of 1a was treated with 10% of SbCl₅, at -70°C (entry 1, Table 1), followed by the addition of an excess of diene 2a. After completion of the reaction, about 2 h, the mixture was isomerized and oxidized, to eliminate the problem of endo/exo stereoisomers, and furnished 3a and 4a in a ratio of 90:10, significantly better than the 70:30 obtained with BF₃ under similar conditions (entry 2); from this mixture, pure **3a** could be isolated by simple crystallization. This result suggests that complexation on the less hindered carbonyl-4 of 1a has increased with SbCl₅. Entry 3 presents the uncatalyzed DA reaction and confirms the results described in the literature.^{1,2} It is worth mentioning that experiments were also carried out using $TiCl_4$ (entry 4), under the same conditions, giving a 38:62 ratio of **3a:4a**, similar to the uncatalyzed reaction. This unexpected effect of TiCl₄ catalysis in DA reactions has been observed in other cases and is not completely understood.⁶ The adsorption effects of SiO₂ in DA reactions were also tested in entry 5: although the reaction rate was enhanced, we observed a 33:67 ratio of 3a:4a ratio, which is very similar to that for the uncatalyzed reaction.

Since synthesis of 2,5-dimethyl-1,4-naphthoquinone, 3a, could be improved by SbCl₅ catalysis, we started investigations with similar diene/dienophile systems, under

the same conditions as entry 1. Entry 6 represents the DA reaction between hexadiene **2b** and **1a**, catalyzed by $SbCl_5$, yielding a 95:05 ratio of **3b:4b**. The same reaction catalyzed by BF₃ (entry 7) gave an 87:13 ratio of **3b:4b**. This result indicates a preference for a less hindered arrangement diene-dienophile-LA in the transition state as the LA becomes larger. In comparison, the thermal reaction was completely unselective (entry 8).

On the other hand, increasing the size of the substituent in the quinone, as in 1c, the same single product was obtained in the catalyzed and uncatalyzed reactions (entries 9–11). Its structure 3c ('*meta*') was deduced by a comparison of the ¹H NMR data with known naphthoquinones of the same substitution pattern. Steric demand in 1c is such that both catalysts were forced to complex at the carbonyl-4, causing the exclusive formation of 3c. In the thermal reaction, it seems that steric factors become more important than electronic ones, since no trace of the '*ortho*' product 4c was detected. The SbCl₅ catalyzed reaction between isoprene and 1a did not result in better selectivity than the thermal reaction and produced high amounts of polymeric material.

In conclusion, the use of $SbCl_5$ can enhance the regioselectivity in DA reactions when steric and electronic factors compete in the transition state. Our results should encourage further applications in regioselective LA-catalyzed reactions.

•	Entry	Diene	Dienophile	Catalyst ^a	°C	Time	3:4	Yield % ^b
	1	2a	1a	SbCl ₅ (10%)	-70	2 h	90:10	45
	2	I	0	BF ₃ (15%)	-70	5 h	70:30	c
	3			No catalyst	100	48 h	30:70	50
	4		ő	TiCl ₄ (10%)	-70	2 h	38:62	40
	5			${\rm SiO_2}^{\sf d}$	-50	7 d	33:67	c
	6	2b	0 1a	SbCl ₅ (10%)	-70	2 h	95:05	45
	7			BF ₃ (10%)	-70	5 h	87:13	40
	8	Ŵ	U O	No catalyst	100	24 h	46:54	50
	9	2a	0 lc	SbCl ₅ (10%)	-70	2 h	100:0	40
	10			BF ₃ (10%)	-70	4 h	100:0	40
	11	1	Щ Г	No catalyst	100	48 h	100:0	50

 Table 1. DA reactions in toluene of 1,4-dienes and -benzoquinones

^a molar ratio in relation to benzoquinone;

^b crude product after oxidation;

^c not determined.

^d 2 g of SiO₂ / mmol of 1a.

Typical procedures

Catalyzed reaction: A solution of 1 mmol of 1 in 5 mL of toluene was treated with 0.1 mmol of LA, at -70° C, followed by the slow addition of 4 mmol of 2. After 2 hours, at -70°C, 0.5 mL of HCl (1N) and 5 mL of cold H₂O were added. After extraction and evaporation of toluene, the residue was dissolved in 5 mL of concentrated HOAc and refluxed for 30 min. A solution of 2 g of CrO₃, in 5 mL of H₂O, was slowly added at 70°C. After 15 min, at 70°C, this mixture was poured over 10 g of ice. Crystals were formed in entries 1-5 and 9-11, which were filtered and dried. In entries 6-8, the oily product was extracted with hexane. These crude materials were analyzed by GC (5% phenylmethylsilicone, 95% methylsilicone) and ¹H NMR (in benzene) for the determination of the isomeric ratios.

Thermal reaction: 1 mmol of 1, 2 mmol of 2 and 5 mL of toluene were mixed in a glass tube, which was quickly sealed. After 2 days, at 100°C, the tube was opened and the solvent and diene excess were eliminated under vacuum. Oxidation, hydrolysis and analysis of isomer proportion were performed as described above. **3b**: oil; ¹H NMR (300 MHz, C_6D_6) δ 0.93 (3H, t, J = 7.5 Hz), 1.38 (3H, d, J = 1.5 Hz), 2.86 (2H, q, J = 7.5 Hz), 5.97 (1H, q, J = 1.5 Hz), 6.67 (1H, dd, J = 7.8, 1.8 Hz), 6.72 (1H, dd, J = 7.8, 7.8 Hz), 7.73 (1H, dd, J = 7.8, 1.8 Hz) ppm. **4b**: oil; δ 0.89 (3H, t, J = 7.5 Hz), 1.33 (3H, d, J = 1.5 Hz), 2.80 (2H, q,

J = 7.8, 1.8 Hz), 6.75 (1H, dd, J = 7.8, 7.8 Hz), 7.69 (1H, dd, J = 7.8, 1.8 Hz) ppm. 3c: yellow crystals; mp 86°C; δ 1.18 (9H, s), 2.68 (3H, s), 6.60 (1H, s), 6.89 (1H, dd, *J* = 7.5, 0.6 Hz), 6.97 (1H, dd, *J* = 7.5, 7.5 Hz), 8.00 (1H, dd, J = 7.5, 0.6 Hz) ppm.

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