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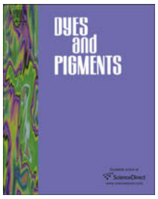

Rapid, efficient and one pot synthesis of anthraquinone derivatives catalyzed by Lewis acid/methanesulfonic acid under heterogeneous conditions

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ABSTRACT

A new reagent combination for the direct preparation of anthraquinone derivatives from the reaction of various benzene derivatives with phthalic anhydride in the presence of Lewis acid/methanesulfonic acid (LAMA) is reported. In this reaction, the products were obtained in high yields and short reaction times under heterogeneous conditions. The effect of aromatic ring substituents on the outcome of the reaction has been studied. Benzenes that contain electron withdrawing substituents have the lowest reactivity in this reaction. The advantages of this method include: one pot reaction, simplicity, good efficiency, easy reaction work-up and availability of the starting materials. The structures of products were assigned by physical data and spectroscopic methods.

1. Introduction

Anthraquinone and its hydroxyl and amino derivatives are of considerable practical significance in pharmacology, biochemistry and dye industry. Anthraquinone dyes are used for coloration of cotton and cellulose fibers as well as of hydrophobic, synthetic materials [1]. The hydroxylated 9,10-anthraquinones occur widely in nature and are known to display various pharmacological activities [2].

Several families of antitumour natural products, including the anthracyclines (e.g. doxorubicin and daunorubicin) [3], the pluramycins e.g. sapurimycin [4] and some of the enediyne antibiotics, like dynemycin A and deoxydynemycin A [5] contain a 9,10-anthraquinone substructure.

Anthraquinone is insoluble in water and must be dissolved in ethanol or other solvents. Also the quinone system is electroactive both in acetonitrile and in aqueous solutions up to pH 11 [6]. Anthraquinone redox active moieties have been used as the switching antennae for enhanced cation binding [7–10]. This group undergoes two successive monoelectronic reductions, first to the anion radical and then to the dianion [11].

In the foregoing reports the reaction conditions employed for the synthesis of the anthraquinones are usually severe, starting materials are often not commercially available and the routes typically employ two independent steps with a long reaction times and low yields.

In order to overcome these limitations, we report a new approach for the synthesis of anthraquinone derivatives from the reaction of aromatic compounds with phthalic anhydride in the presence of a Lewis acid/methanesulfonic acid combination as catalyst under heterogeneous conditions.

2. Experimental

2.1. Materials

Chemicals were purchased from the Merck Chemical Company in high purity. All materials were of commercial reagent grade. The phthalic anhydride and benzene derivatives were purified by standard procedures.

2.2. Apparatus

IR spectra were recorded in KBr pellets on a Perkin–Elmer 781 Spectrophotometer and an Impact 400 Nicollet FTIR Spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Bruker DRX-400 Spectrometer (Germany) using TMS as an internal reference. Melting points were obtained with a Yanagimoto micro melting point apparatus. The purity

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determination of the substrates and reactions monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

2.3. General procedure for the synthesis of anthraquinone derivatives

Phthalic anhydride (1 g, 6.75 mmol) and the substituted benzene (6.75 mmol) were mixed together and then anhydrous aluminum trichloride (0.1 g, 0.75 mmol) and concentrated methanesulfonic acid (5 ml, 0.08 mmol) was added to this mixture. The stirred reaction mixture was heated at 95–100 °C by stirring for the 15–65 min. The progress of the reactions was followed by TLC. After completion of the reaction, reaction mixture was poured on crushed ice and extracted with dichloromethane (3 × 30 ml). The organic layer was washed with 5% sodium hydrogen carbonate solution (100 ml) and dried with $CaCl_2$. The solvent was evaporated to give anthraquinone derivatives as crystalline solid, which was recrystallized from acetone and distillated water to give anthraquinone derivatives as products in 6–93% yields.

*2.3.1. 1,4-Dihydroxy-9,10-anthraquinone (**3a**)*

$C_{14}H_8O_4$, red solid, 93% yield, MW = 240, mp = 194–196 °C (lit [12] mp = 194 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2919 (w), 2847 (w), 1629 (m), 1588 (m), 1454 (m); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 7.0–7.3 (2H, s), 7.6–7.8 (2H, s), 8.1–8.3 (2H, s), 12.6–12.8 (2H, s); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 114, 128, 131, 135, 136, 159, 188.

*2.3.2. 1,3-Dihydroxy-9,10-anthraquinone (**3b**)*

$C_{14}H_8O_4$, orange solid, 91% yield, MW = 240, mp = 268 °C (lit [12] mp = 268–270 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 3216 (s), 1613 (s), 1529 (s), 1434 (s), 1250 (m); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 6.71 (1H, s), 7.4 (1H, s), 7.8 (2H, s), 8.3 (2H, s), 12.4 (2H, s); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 107, 108, 109, 126, 127, 132, 133, 134, 135, 164, 165, 181, 185.

*2.3.3. 2,3-Dihydroxy-9,10-anthraquinone (**3c**)*

$C_{14}H_8O_4$, yellow solid, 92% yield, MW = 240, mp = 259–262 °C (lit [13] mp = 260 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2986 (s), 2514 (w), 2953 (w), 1690 (s), 1582 (m); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 7.5 (2H, s), 7.7–7.9 (2H, m), 8.2–8.3 (2H, m), 9.3 (2H, s); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 112, 127, 128, 133, 134, 153, 182.

*2.3.4. 1,4-Dimethyl-9,10-anthraquinone (**3d**)*

$C_{16}H_{12}O_2$, yellow solid, 89% yield, MW = 236, mp = 134–137 °C (lit [14] mp = 141 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2960 (m), 2924 (m), 1659 (s), 1588 (m), 1380 (m), 1300 (s), 1250 (s); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 2.57 (6H, s), 7.2 (2H, s), 7.51–7.53 (2H, q), 7.94–7.97 (2H, q); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 23, 128, 133, 134, 135, 138, 141, 187.

*2.3.5. 1,3-Dimethyl-9,10-anthraquinone (**3e**)*

$C_{16}H_{12}O_2$, yellow solid, 90% yield, MW = 236, mp = 158–161 °C (lit [14] mp = 172 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2975 (w), 2909 (w), 1659 (s), 1588 (s); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 2.24 (3H, s), 2.58 (3H, s), 7.5–7.6 (1H, m), 7.8 (2H, s), 8–8.1 (3H, m); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 22, 23, 127, 128, 130, 134, 135, 136, 137, 140, 143, 145, 185, 186.

Table 1
The reaction of toluene and phthalic anhydride in the presence of various Lewis acids/methanesulfonic acid as catalyst.

Entry	L.A	Temperature (°C)	Time (min)	Yield (%)
1	Fecl$_3$	130–136	60	–
2	$SnCl_4$	150–160	60	20
3	$AlCl_3$	95–100	40	80
4	$ZnCl_2$	150–160	60	5
5	P_2O_5	150–160	60	–
6	None	150	>180	–

*2.3.6. 2,3-Dimethyl-9,10-anthraquinone (**3f**)*

$C_{16}H_{12}O_2$, yellow solid, 85% yield, MW = 236, mp = 148–152 °C (lit [15] mp = 150 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2975 (w), 2909 (w), 1664 (s), 1588 (s), 1380 (w), 1350 (s); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 2.2–2.53 (6H, s), 7.7–7.8 (4H, m), 8.3–8.4 (2H, s); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 18, 123, 127, 130, 132, 134, 142, 181.

*2.3.7. 2-t-Butyl-9,10-anthraquinone (**3g**)*

$C_{18}H_{16}O_2$, dark green solid, 82% yield, MW = 264, mp = 85–88 °C (lit [16] mp = 89 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2955 (m), 1664 (s), 1582 (s), 1450 (m); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 1.19–1.21 (9H, s), 7.55–8.5 (7H, m); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 32, 38, 125, 128, 129, 133, 134, 135, 136, 159, 184, 185.

*2.3.8. 2-Methyl-9,10-anthraquinone (**3h**)*

$C_{15}H_{10}O_2$, yellow solid, 80% yield, MW = 222, mp = 176–178 °C (lit [17] mp = 177–179 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2950 (w), 2900 (w), 1669 (s), 1593 (s), 1326 (s), 1291 (s); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 2.4–2.7 (3H, s), 7–8.5 (7H, m); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 20, 125, 126, 130, 132, 133, 134, 145, 180, 183.

*2.3.9. 2-Bromo-9,10-anthraquinone (**3i**)*

$C_{14}H_7BrO_2$, yellow solid, 53% yield, MW = 287, mp = 205–207 °C (lit. [13] mp = 207 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 3067 (w), 1675 (s), 1572 (s); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 7.06–8.39 (7H, m); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 128, 131, 132, 133, 135, 136, 137, 138, 184.

*2.3.10. 2-Chloro-9,10-anthraquinone (**3j**)*

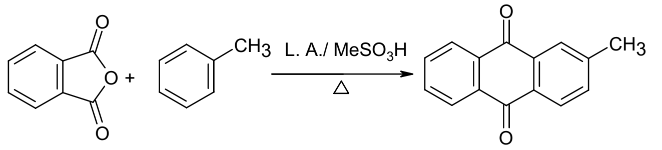
$C_{14}H_7ClO_2$, pale yellow solid, 26% yield, MW = 242, mp = 208–210 °C (lit [18] mp = 211 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 1680 (s), 1582 (s), 1300 (m), 1280 (s); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 7.41–7.96 (7H, m); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 127, 129, 132, 133, 134, 135, 140, 182.

*2.3.11. 1,4-Dibromo-9,10-anthraquinone (**3k**)*

$C_{14}H_6O_2$, yellow solid, 15% yield, MW = 206, mp = 221–223 °C (lit [13] mp = 225 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2985 (w), 1654 (s), 1581 (m), 1290 (s); ^1H NMR (400 MHz), $CDCl_3/\delta$ ppm: 7.02–7.10 (2H, s), 7.4–7.65 (2H, s), 7.8–8.1 (2H, s); ^{13}C NMR (100 MHz), $CDCl_3/\delta$ ppm: 110, 127, 131, 134, 135, 157, 186.

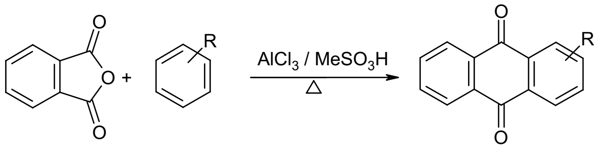
*2.3.12. 2-Nitro-9,10-anthraquinone (**3l**)*

$C_{14}H_7NO_4$, pale yellow solid, 8% yield, MW = 253, mp = 231–234 °C (lit [15] mp = 235 °C), IR (KBr), $\upsilon/\mathrm{cm}^{-1}$: 2975 (w), 1635 (s),



1 2h 3h

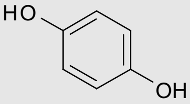
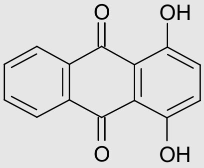
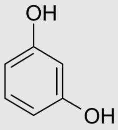
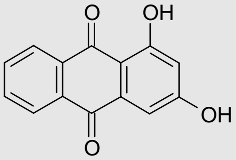
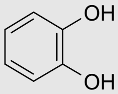
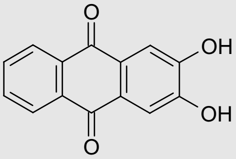
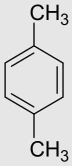
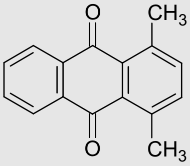
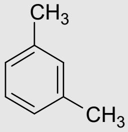
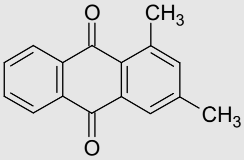
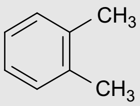
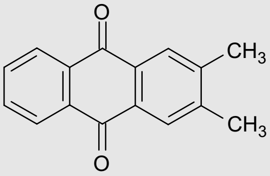
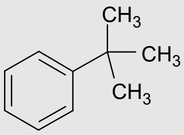
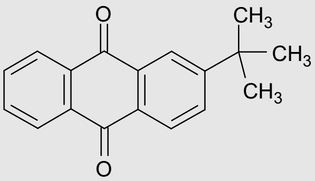
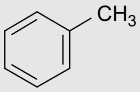
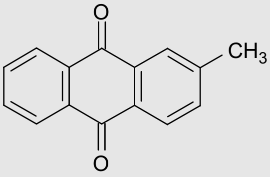
Scheme 1. The reaction of toluene with phthalic anhydride in the presence of L.A./$MeSO_3H$.



1 2a-n 3a-n

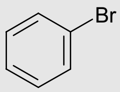
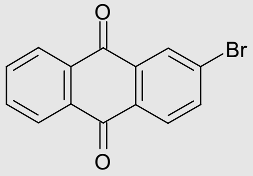
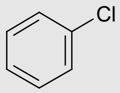
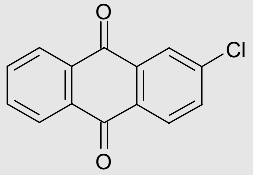
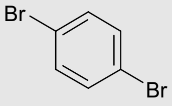
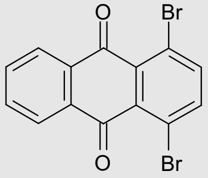
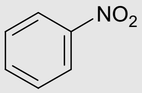
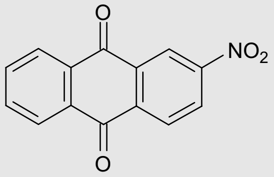
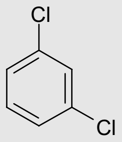
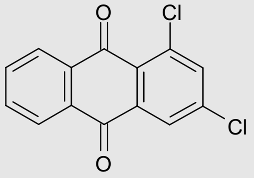
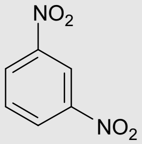
Scheme 2. The reaction of various benzenes with phthalic anhydride catalyzed by $AlCl_3/MeSO_3H$.

Table 2
Synthesis of anthraquinone derivatives from substituted benzene in the presence of aluminum trichloride/methanesulfonic acid.

Entry	Substrate	Product	Time (min)	Yield[a] (%)
1			15	93
2			15	91
3			15	92
4			25	89
5			25	90
6			25	85
7			37	82
8			40	80

(*continued on next page*)

Table 2 (*continued*).

Entry	Substrate	Product	Time (min)	Yield[a] (%)
9			50	53
10			55	26
11			65	15
12			65	8
13			65	6
14		–	Overnight	–

[a] Isolated yields based on benzene derivative.

1592 (s), 1310 (m); ^{1}H NMR (400 MHz), CDCl$_3$/δ ppm: 7.05–7.45 (4H, m), 8.10–8.41 (3H, m); ^{13}C NMR (100 MHz), CDCl$_3$/δ ppm: 129, 132, 133, 135, 137, 138, 140, 141, 189.

2.3.13. *1,3-Dichloro-9,10-anthraquinone (3m)*

$C_{14}H_6O_2Cl_2$, yellow solid, 6% yield, MW = 277, mp = 167–169 °C (lit [18] mp = 171 °C), IR (KBr), ν/cm^{-1}: 2987 (m), 2909 (w), 1645 (s), 1565 (s), 1310 (m); ^{1}H NMR (400 MHz), CDCl$_3$/δ ppm: 7.01–7.2 (4H, m), 7.5–7.6 (1H, s), 7.8 (1H, s); ^{13}C NMR (100 MHz), CDCl$_3$/δ ppm: 107, 110, 125, 127, 131, 142, 184.

3. Results and discussion

In this study, the reactions of toluene with phthalic anhydride were carried out by heating in the presence of some Lewis acids as catalyst (Scheme 1).

A variety of Lewis acids were employed in this reaction in order to examine their catalytic effect. When 1 mol toluene was treated with 1 mol phthalic anhydride, a mixture of Lewis acid/methanesulfonic acid (0.11/0.012 mol) was added to it. In this reaction, 2-methyl-9,10-anthraquinone (**3h**) was obtained. The results from the reactions examined are presented in Table 1.

As can be seen in Table 1, in these reactions, the 9,10-anthraquinone product was prepared in high yield and short reaction time in the presence of AlCl$_3$/MeSO$_3$H as the best catalyst among the other studied catalysts (Table 1, entry 3).

However, when the reaction was undertaken in the absence of catalyst no anthraquinone product was obtained even an extension of the reaction time up to 180 min (Table 1, entry 6). It is of great importance that various catalysts largely affect the reaction.

In order to develop and extend this method, various benzene derivatives have been reacted with phthalic anhydride in the presence of $AlCl_3/MeSO_3H$ as the heterogeneous catalyst (Scheme 2). The corresponding results are summarized in Table 2.

In these reactions, the optimum amount of the catalyst used for all substrates was 0.1 mol for 1 mol of benzene derivative. As shown in Table 2, the reaction of substrates with electron donating substituents with phthalic anhydride proceeds in high yields and short reaction times (Table 2, entries 1–8). While the reaction of substrates with electron withdrawing substituents resulted in only low yields of the anthraquinone products after long reaction times (Table 2, entries 9–12). In the reaction with *m*-dinitrobenzene no product resulted even on continuation of the reaction overnight.

The structure of the anthraquinone derivatives was assigned by physical and spectroscopic data. In the ^{13}C NMR spectra, atoms of the carbonyl groups appear in the range $\delta = 181–188$ ppm the aromatic carbon atoms in the range $\delta = 122–140$ ppm and aliphatic carbon atoms in $\delta = 18–38$ ppm. ^{13}C NMR spectroscopy supported the symmetrical structure of the compounds e.g. **3a**, **3c**, **3d**, **3f** and **3k** with the presence of fewer signals in the spectra than were expected for the alternate non-symmetrical products. The structure of the products was further supported by ^{1}H NMR spectroscopy. The protons of alkyl groups have chemical shifts in the range $\delta = 1.3–3.3$ ppm. The signal around $\delta = 6.5–8.4$ ppm are assigned by protons of HC═CH of aromatic rings.

In the IR spectra, the stretching vibration of C═O in the carbonyl groups appear at region between $\upsilon = 1610–1690\ cm^{-1}$ typical for 9,10-anthraquinones. The hydroxyl group, O–H bond stretching frequency in compounds is found in the region between $\upsilon = 3150–3400\ cm^{-1}$ as a strong broad band.

4. Conclusions

The reaction between phthalic anhydride and benzene derivatives in the presence of aluminum chloride and concentrated methanesulfonic acid gave anthraquinone derivatives directly. The advantages of this new reagent combination include one pot direct formation of anthraquinones, good yield, short reaction times and simple work-up.

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