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Research Article

Substituent Effects on Regioselectivity of the Diels-Alder Reactions: Reactions of 10-Allyl-1,8-dichloroanthracene with 2-Chloroacrylonitrile, 1-Cyanovinyl Acetate and Phenyl Vinyl Sulfone

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Diels-Alder reaction of 10-allyl-1,8-dichloroanthracene (**3**) with 2-chloroacrylonitrile (**4**) and 1-cyanovinyl acetate (**5**) gives exclusively the *ortho* isomer while its reaction with phenyl vinyl sulfone (**10**) yields a mixture of two isomeric adducts with priority to *ortho* isomer. The reactions proceeded under microwave condition in xylene. Configurations of these isomers have been assigned with the help of NMR spectra. The results indicated that the steric effect is dominating toward the isomer regioselectivity in the Diels-Alder reaction of the present compounds.

1. Introduction

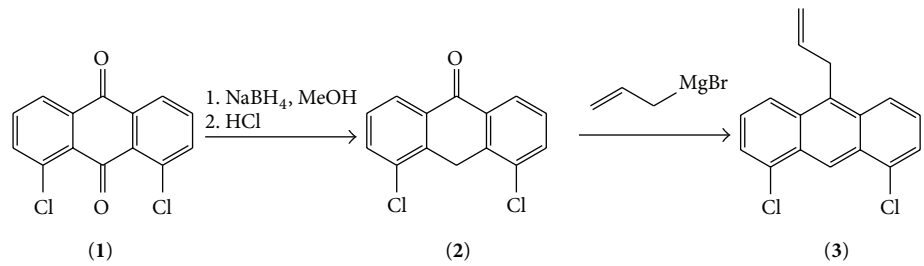
The Diels-Alder reaction is considered one of the most useful synthetic reactions and it is among the most atom economical and reliable carbon-carbon bond forming methods known in organic chemistry [1]. In this reaction, a conjugated diene the 4π component (diene) reacts with an alkene, the 2π component (dienophile) to build up six-member system. The importance of the Diels-Alder reaction arises from its reliability, versatility, and remarkable regio-stereoselectivity. Among all the dienes, anthracene derivatives have attracted considerable interest as one of the powerful dienes and their ability to react with various dienophiles through Diels-Alder reactions has been extensively investigated [2–11].

The Diels-Alder addition ethylene or ethylene equivalent to 9-substituted anthracene precursor was the key steps for the synthesis of some antidepressant and anxiety drugs such as benzoctamine, maprotiline, and homologues of these compounds [12–19].

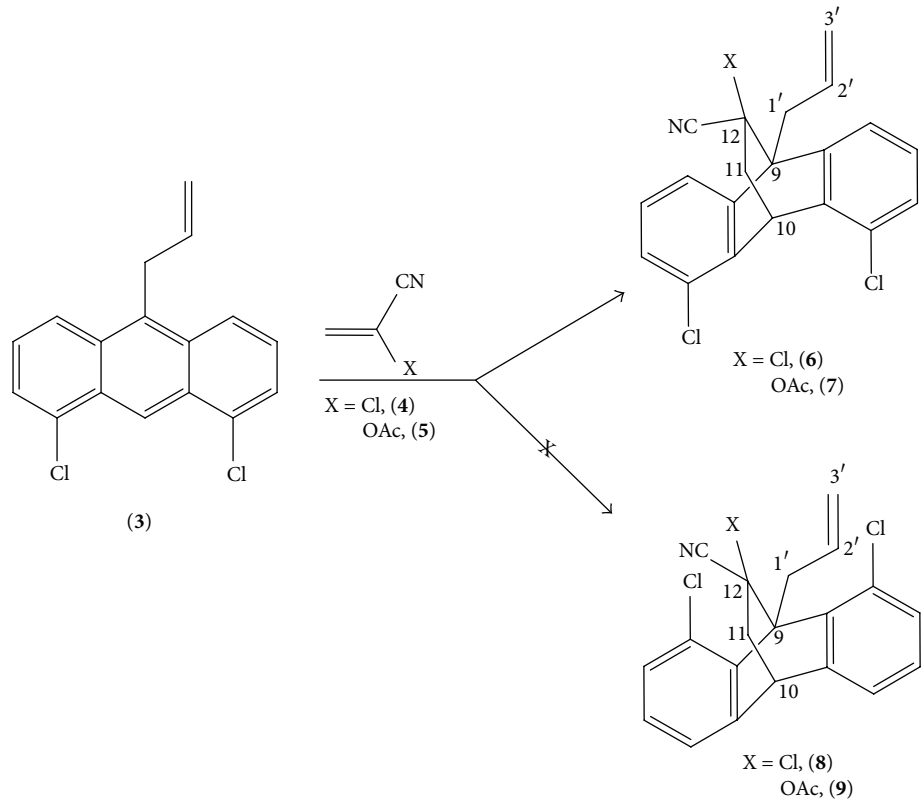
The substituted anthracenes could be interesting targets for the study of regioselectivity and stereoselectivity in the Diels-Alder reactions. The investigation of the substituents effect on the Diels-Alder reaction of 10-allyl-1,8-dichloroanthracenes with dienophiles has not been reported yet. In this work, the regioselectivity of the Diels-Alder reaction of 10-allyl-1,8-dichloroanthracenes (**3**) with 2-chloroacrylonitrile (**4**), 1-Cyanovinyl acetate (**5**), and Phenyl vinyl sulfone (**10**) has been studied. The structural elucidation of the cycloadducts has been made based on the NMR spectroscopic data.

2. Results and Discussion

The reduction of the starting material 1,8-dichloroanthraquinone (**1**) to afford 4,5-dichloroanthrone (**2**) was the first step toward the forward synthesis of the targets substituted-10-allyl-1,8-dichloro-9,10-dihydro-9,10-ethanoanthracene (**6**, **7**, **11**, **12**). The intermediate 10-allyl-1,8-dichloroanthracene (**3**) was prepared as described in the literature [20], since allylmagnesium bromide reacted with 4,5-dichloroanthrone (**2**) which was prepared based on the procedure reported by Goichi et al. [21] (Scheme 1).



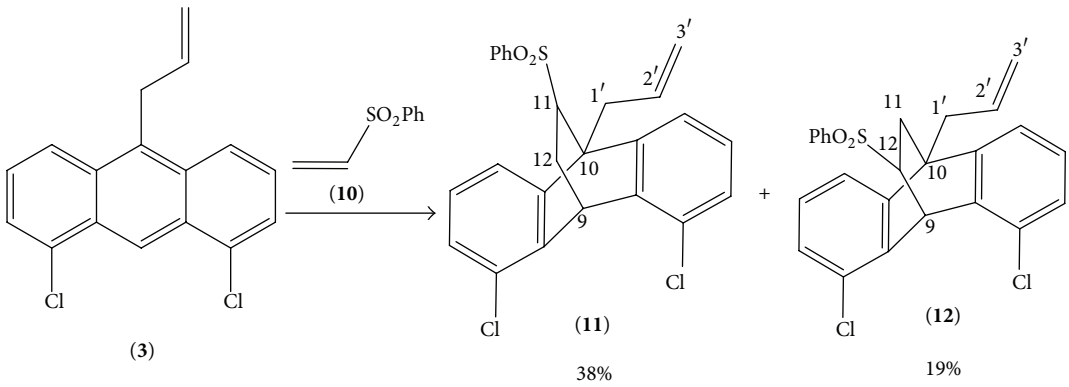
Scheme 1: Preparation of the intermediate 10-allyl-1,8-dichloroanthracene (**3**).



Scheme 2: The Plausible Diels-Alder reaction of the ethylene equivalents (**4**) and (**5**) with 10-allyl-1,8-dichloroanthracene (**3**).

In continuation to our interest in anthracene derivatives [19, 22]. Herein, we want to report our studies on the Diels-Alder reaction of 10-allyl-1,8-dichloroanthracene (**3**) with 2-chloroacrylonitrile (**4**), 1-cyanovinyl acetate (**5**), and phenyl vinyl sulfone (**10**). The Diels-Alder reaction between 10-allyl-1,8-dichloroanthracene (**3**) and ketene equivalent 2-chloroacrylonitrile (**4**) proceeded smoothly under microwave condition to give only one isomer (**6**) in 95% yield, and the reaction of 10-allyl-1,8-dichloroanthracene (**3**) with 1-cyanovinyl acetate (**5**) under the same conditions afforded 85% of the isomer (**7**) (Scheme 2). Despite the nature difference between chlorine as an electron withdrawing atom and acetate as an electron donating group, their effect as substituents beside the nitrile group on the dienophile is in the same direction and apparently favored toward the formation of the one isomer. It is clear that chlorine and acetate substituents on the dienophile exhibited no steric effect, subsequently the formation of the other putative isomers (**8**) and (**9**) is not favored.

The nature of the diene and dienophile substituent has been successfully exploited in assigning the configuration and regioselectivity of various Diels-Alder adducts [23, 24], and when employed to our adducts this effect discloses considerable information. The ^{1}H-NMR of the isomer (**6**) exhibited a downfield triplet signal, as result of chlorine effect, at δ 5.49 ppm with coupling constant J 2.9 Hz; this signal integrated for the bridge-head proton H-10. Due to the bending of the isomer as demonstrated by the crystal structure, the two protons assigned for C11 were nonequivalent and displayed two double doublet signals regions at δ 2.38 and 2.85 ppm.



Scheme 3: The Diels-Alder cycloaddition of phenyl vinyl sulfone (**10**) with 10-allyl-1,8-dichloroanthracene (**3**).

The structural elucidation of the isomer (**7**) by ^{1}H-NMR and ^{13}C-NMR is similar, with small variation in chemical shifts, to the isomer (**6**).

The Diels-Alder reaction, where the formation of more than one isomer is possible, has been studied. The Diels-Alder reaction between 10-allyl-1,8-dichloroanthracene (**3**) and phenyl vinyl sulfone (**10**) led to isomers (**11**) and (**12**) as regioisomers in 57% yield under microwave conditions in xylene. The isomers were easily separated by silica gel column chromatography with the eluent system ethyl acetate : petroleum ether (1 : 5). The reaction favours the formation of the *ortho* isomer (**11**), the ratio of the isomers (*ortho* : *meta*) was 2 : 1. This isomers ratio indicated that the transition state containing the phenyl sulfone functionality above the chlorine atom is less stable than the other possibility (Scheme 3).

The obtained isomers are due to the fact that both the 10-allyl-1,8-dichloroanthracene (**3**) (diene) and phenyl vinyl sulfone (**10**) (dienophile) are unsymmetrical. It is noteworthy to mention the big size of the phenyl group on the dienophile (**10**), so its steric effect enforces the formation of the *meta* isomer (**12**) in contrast to dienophiles (**4**) and (**5**), where the substituents effect led to no formation of the putative isomer isomers (**8**) and (**9**).

The assignment of the *ortho* isomer (**11**) and the *meta* isomer (**12**) by ^{1}H-NMR analysis was not troublesome. The ^{1}H-NMR results could unambiguously distinguish between the regioisomers; the bridge-head proton H-9 of the *ortho* isomer (**11**) has triplet signal appearing at δ 5.4 ppm with coupling constants J = 2.9 Hz whereas the bridge-head proton H-9 of *meta* isomer (**12**) has doublet signal at 5.57 ppm with coupling constants J = 1.4 Hz integrated, respectively. The downfield shifting of the H-9 in the *meta* isomer (**12**) is a result of deshielding effect of the phenyl sulfone group, since this group is more closer to H-9 in case of *meta* isomer (**12**).

3. Experimental

3.1. Synthesis of 4,5-Dichloroanthracene-9-one (2). To a stirred suspension of the 1,8-dichloroanthraquinone (**1**) (10 g, 36.10 mmol) in methanol (720 mL), $NaBH_4$ (6.8 g, 180 mmol) was added slowly in small portions over 5 h and the solution was further stirred for 1 h at room temperature. 90 mL of the conc. HCl was added and the reaction mixture was refluxed for 1 h and then cooled to room temperature. The formed solid was filtered through suction funnel, washed with H_2O, and air-dried. This crude product was purified via flash column chromatography on silica gel using CH_2Cl_2/hexane (1 : 10 and then 1 : 1) to afford (**2**).

Yield 89%; yellow powder; m.p. 192°C. IR (KBr): ν = 3433, 3078, 2925, 1659, 1584, 1446, 1391, 1312, 1130, 961, 871, 741, 660 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 4.15 (s; 2H, *H*-10), 7.41 (t; J = 8.0, 2H, Ar*H*), 7.64–7.66 (m, 2H, Ar*H*), 8.24 (dd; J = 1.4, 1.4 Hz, 2H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.3, 126.2, 128, 132.7, 133.6, 134, 137.2, 182.5 ppm. MS (EI): *m/z* (%) = 262 (35) [M$^+$], 229 (27), 227 (100), 199 (27), 163 (48). HRMS (EI): Calcd. For $C_{14}H_8OCl_2$ [M$^+$] 261.9952, Found 261.9954.

3.2. Synthesis of 10-Allyl-1,8-dichloroanthracene (3). A two-neck round-bottom flask containing 4,5-dichloroanthrone (**2**) (5 g, 19 mmol) was equipped with a magnetic stirrer, a rubber septum-sealed funnel connected with side joint and the other joint was connected to a balloon of nitrogen. The flask was evacuated and flushed with nitrogen two times; then 80 mL of dry THF was injected into the flask. The solution was cooled to 0°C and allylmagnesium bromide (1.0 M in Et_2O, 25 mL, 25 mmol) was added dropwise. The solution was then stirred at room temperature for 1 h and quenched with 1 M HCl (120 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined organic solution was dried over $Na_2SO_4$and then evaporated the solvent. The residue was redissolved in 80 mL of toluene and 10 g of P_2O_5 was added. The mixture was stirred for 1.5 h. Then, it was poured slowly over 160 mL of $NaHCO_3$, extracted with Et_2O (2 × 100 mL), washed with 200 mL of water, dried over Na_2SO_4, and evaporated. The residue obtained was purified via flash column chromatography on silica gel using hexane and then hexane/CH_2Cl_2 90 : 10 to afford (**3**).

Yield 55%; yellow powder; m.p. 105°C. IR (KBr): ν = 3074, 2980, 1751, 1619, 1433, 1335, 1219, 1065, 914, 873, 791, 728 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 4.21 (d; J = 5.1 Hz, 2H, *H*-1′), 4.75 (dd; J = 1.4, 16.8 Hz, 1H, *H*-3′),

4.97 (dd; J = 1.4, 10.2 Hz, 1H, H-3′), 6.0–6.10 (m; 1H, H-2′), 7.31 (t; J = 8.0 Hz, 2H, ArH), 7.51 (d; J = 7.3 Hz, 2H, ArH), 8.01 (d; J = 8.8 Hz, 2H, ArH), 9.16 (s, 1H, H-9) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 32.4, 116.4, 120.3, 123.6, 125.5, 125.6, 129.1, 130.9, 133.0, 133.1, 135.7 ppm. MS (EI): m/z (%) = 286 (9) [M^+], 263 (7), 219 (60), 131 (39), 100 (4), 69 (100). HRMS (EI): Calcd. For $C_{17}H_{12}Cl_2$ [M^+] 286.0317, Found 286.0316.

3.3. General Synthesis of Substituted-10-Allyl-1,8-dichloro-9,10-dihydro-9,10-ethanoanthracene. An oven-dried 10 mL microwave reaction vessel containing a stir bar was charged with a solution of 10-allyl-1,8-dichloroanthracene (**3**) (6 mmol) in (3.5 mL) xylene and dienophile reagent (7.2 mmol). The vessel was sealed with a plastic microwave septum. The vessel was placed into the Microwave CEM Discover SP system under the following conditions: stirring was set high. Power max was kept on. Maximum power and maximum pressure were set 250 W and 250 psi, respectively, with a set temperature of 150°C for 40 h. After microwave irradiation was complete, the mixture was cooled to room temperature and the solvent removed in vacuo. The residue was purified via column chromatography on silica gel using ethyl acetate/petroleum ether (1 : 5) to afford the corresponding cycloadduct.

*3.3.1. 9-Allyl-4,5,12-trichloro-9,10-dihydro-9,10-ethanoanthracene-12-carbonitrile (**6**).* Yield 79%; pale yellow powder; m.p. 180°C. IR (KBr): ν = 3073, 2925, 2856, 2235, 1731, 1579, 1446, 1236, 1093, 979, 923, 790 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 2.38 (dd, J = 2.9, 13.9 Hz, 1H, H-11), 2.85 (dd, J = 2.9, 14.6 Hz, 1H, H-11), 3.55–3.61 (m, 1H, H-1′), 3.73–3.80 (m, 1H, H-1′), 5.47 (dd; J = 1.4, 17.6 Hz, 1H, H-3′), 5.34 (dd, J = 1.4, 10.2 Hz, 1H, H-3′), 5.49 (t; J = 2.9 Hz, 1H, H-10), 5.92–6.01 (m; 1H, H-2′), 7.17–7.22 (m; 2H, ArH), 7.31–7.34 (m; 2H, ArH), 7.41 (d; J = 7.3 Hz, 1H, ArH), 7.48 (d; J = 7.3, 1H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.0, 35.7, 35.9, 47.5, 54.6, 60.7, 118.3, 129.7, 129.8, 133.5, 138.4, 138.6, 139.1, 139.7 ppm. MS (EI): m/z (%) = 373 ([M^+], not recorded), 339 (22), 337 (27), 326 (43), 304 (52), 286 (100), 251 (58), 216 (44), 215 (49), 89 (41), 87 (88).

*3.3.2. 9-Allyl-4,5-dichloro-12-cyano-9,10-dihydro-9,10-ethanoanthracen-12-yl acetate (**7**).* Yield 84.3%; white powder; m.p. 202°C. IR (KBr): ν = 3079, 2983, 2853, 1751, 1639, 1445, 1371, 1227, 1014, 920, 781 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 1.94 (s, 3H, CO_2CH_3), 1.98 (d; J = 2.9 Hz, 1H, H-11), 2.8 (dd, J = 2.9, 2.9 Hz, 1H, H-11), 3.59–3.62 (m, 2H, H-1′), 5.31 (dd; J = 1.4, 10.2 Hz, 1H, H-3′), 5.43–5.49 (m; 2H, H-10, H-3′), 5.97–6.07 (m; 1H, H-2′), 7.14–7.20 (m; 2H, ArH), 7.25–7.31 (m; 2 H, ArH), 7.42 (d; J = 7.3 Hz, 1H, ArH), 7.49 (d; J = 8.0 Hz, 1H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 30.3, 35.7, 43.5, 53.3, 76.0, 117.1, 118.4, 124.7, 124.9, 127.1, 127.6, 127.7, 128.2, 129.5, 129.8, 133.9, 139.0, 139.1, 139.7, 139.8, 168.6 ppm. MS (EI): m/z (%) = 397 ([M^+], not recorded), 337 (12), 288 (49), 286 (100), 251 (99), 216 (92), 215 (82), 189 (13).

*3.3.3. 10-Allyl-1,8-dichloro-11-(phenylsulfonyl)-9,10-dihydro-9,10-ethanoanthracene (**11**).* Yield 38%; white powder; m.p. 86°C. IR (KBr): ν = 3071, 2935, 2252, 1730, 1635, 1580, 1441, 992, 913, 775, 731, 680, 577 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 0.86–0.95 (m; 2H, H-12), 1.14–1.28 (m; 2H, H-1′), 1.82 (t; J = 11 Hz, 1H, H-11), 5.36 (d; J = 9.5 Hz, 1H, H-3′), 5.4 (t; J = 2.9 Hz, 1H, H-9), 5.54 (d; J = 16.8 Hz, 1H, H-3′), 6.05–6.3 (m; 1H, H-2′), 7.05–7.08 (m; 1H, ArH), 7.13–7.17 (m; 2H, ArH), 7.24–7.26 (m; 1H, ArH), 7.39–7.47 (m; 4H, ArH), 7.52–7.56 (m; 1H, ArH), 7.66–7.68 (m; 2H, ArH) ppm. ^{13}C NMR (DMSO, 100 MHz): δ = 31.1, 33.0, 35.3, 48.0, 54.9, 117.8, 123.2, 126.4, 126.6, 127.2, 127.4, 127.8, 127.9, 128.3, 129.2, 133.6, 135.2, 139.5, 139.7 ppm. MS (EI): m/z (%) = 454 (8) [M^+], 313 (18), 288 (47), 286 (100), 251 (16), 67 (13). HRMS (EI): Calcd. For $C_{25}H_{20}O_2SCl_2$ [M^+] 454.0561, Found 454.0543.

*3.3.4. 10-Allyl-1,8-dichloro-12-(phenylsulfonyl)-9,10-dihydro-9,10-ethanoanthracene (**12**).* Yield 19%; white powder; m.p. 91°C. IR (KBr): ν = 3071, 2969, 2928, 2853, 1634, 1582, 1451, 1312, 1148, 995, 921, 778 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 1.90–1.97 (m; 1H, H-11), 2.01–2.06 (m; 1H, H-11), 3.15–3.23 (m; 2H, H-1′), 3.37–3.42 (m; 1H, H-12), 5.21 (dd; J = 1.4, 10.2 Hz, 1H, H-3′), 5.31 (dd, J = 1.4, 16.8 Hz, 1H, H-3′), 5.57 (d; J = 1.4 Hz, 1H, H-9), 6.05–6.12 (m; 1H, H-2′), 6.96–7.05 (m; 3H, ArH), 7.13–7.18 (m; 3H, ArH). 7.46–7.50 (m; 2H, ArH), 7.56–7.60 (m; 1H, ArH). 7.89–7.91 (m; 2H, ArH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 32.4, 35.5, 37.1, 45.5, 62.9, 119.2, 119.9, 121.1, 126.6, 126.8, 127.3, 127.4, 127.9, 128.7, 129.1, 129.3, 129.5, 131.8, 133.4, 133.7, 136.1, 138.3, 138.4, 139.4, 146.7 ppm. MS (EI): m/z (%) = 454 (8) [M^+], 313 (18), 288 (47), 286 (100), 251 (16), 67 (13). HRMS (EI): Calcd. For $C_{25}H_{20}O_2SCl_2$ [M^+] 454.0561, Found 454.0543.

4. Conclusion

In conclusion, this is the first study reporting the regioselectivity of the Diels-Alder reaction of 10-allyl-1,8-dichloroanthracene with three different-substituted dienophiles. The reactions successfully proceeded under microwave conditions in xylene. The dienophiles, 2-chloroacrylonitrile, and 1-cyanoacetate gave exclusively the *ortho* isomer, while phenyl vinyl sulfone led to the formation of the *ortho* and *meta* isomers with priority to *ortho* isomer. The results indicate that steric effect is dominating in deciding the isomer regioselectivity in the Diels-Alder reaction of the present compounds.

Competing Interests

The authors declare no conflict of interests.

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