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Diels–Alder trapping *vs.* amidoalkylation of cyclopentadiene with polychloroacetaldehyde sulfonylimines

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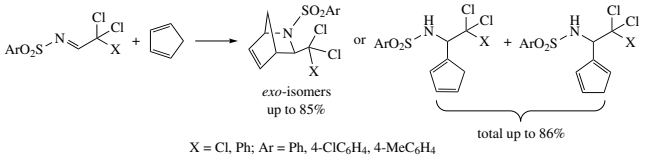
The reaction of chloral or dichloro(phenyl)acetaldehyde *N*-arylsulfonylimines with cyclopentadiene, depending on the reaction conditions, affords either Diels–Alder adducts, 2-arylsulfonyl-2-azabicyclo[2.2.1]hept-5-enes, or unexpectedly new amidoalkylated derivatives of cyclopentadiene, *N*-[(cyclopentadienyl)(polychloromethyl)methyl]arenesulfonamides.



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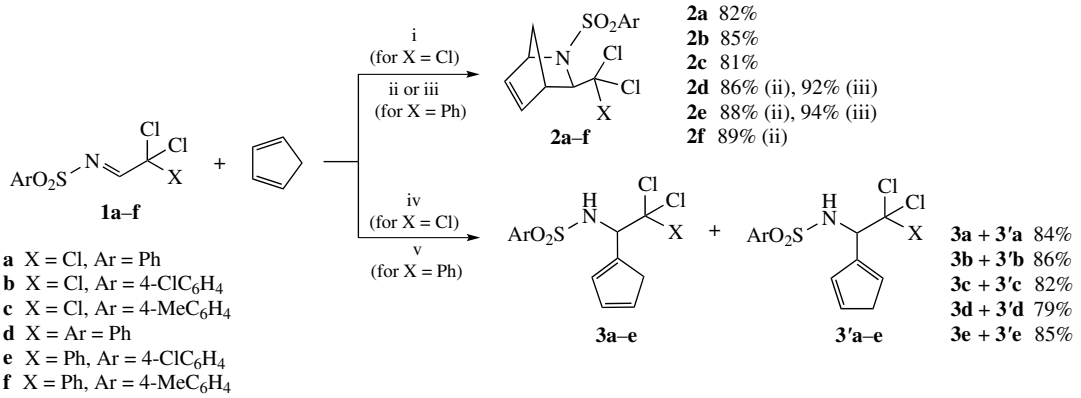
N-Functionally substituted polyhalo ald(ket)imines are valuable reagents for the synthesis of poorly accessible linear and cyclic sulfonamide derivatives.[1] The electrophilic nature of imine group allows one to react them with various nucleophiles and dinucleophiles[1] and perform C-amidoalkylation of (hetero)-aromatic compounds.[1(a),2] Such compounds are promising in the synthesis of diverse heterocyclic derivatives,[3] amino acids,[4] and can be subjected to cycloaddition processes.[1(a)] A classic example of [4+2] cycloaddition with participation of imines is the reaction with cyclopentadiene delivering the corresponding azabicycloheptenes.[5] As previously shown, chloral or fluoral *N*-arylsulfonylimines react with cyclopentadiene in this fashion to produce 2-azabicyclo[2.2.1]hept-5-enes (azanorbornenes) in good yields.[1(a),6] It should be noted that substituted azanorbornenes are of importance for investigation of their biological activity and for further modification providing pharmacophoric N-heterocycles,[7] highly substituted (thio) ureas,[8] and heterocyclic polymers.[9] In this way, the development of chemistry of azabicycloheptene systems is an urgent task. Obviously, synthesis of new functionalized substituted cyclopentadienes, in particular, sulfonamide-containing ones, seems topical.

In the present work, we studied the reactions between polychloroacetaldehyde *N*-arylsulfonylimines **1a–f** and cyclopentadiene (Scheme 1), with dichloro(phenyl)acetaldehyde derivatives **1d–f** having been reacted for the first time. It was unexpectedly found that the reactions afforded not only the expected azanorbornenes **2** (as it was shown previously for imines **1a–c**[6]) but also brought about new unexpected amido(polychloro)ethylated cyclopentadienes **3** (see Scheme 1).

Chloral imines **1a–c** have been synthesized by the reaction of *N*,*N*-dichloroarenesulfonamides with an excess of trichloroethylene.[1(a)] This process occurs selectively to furnish imines **1a–c** in quantitative yields. Therefore, further reaction with cyclopentadiene was carried out in the same trichlorethylene solution. In fact, the reaction of imines **1a–c** with cyclopentadiene was implemented upon heating in an excess of trichlorethylene at 50–70 °C for 5 h to give the anticipated cycloadducts, azanorbornenes **2a–c**, similarly to the previous data.[6(a)–(c)] However, we have unexpectedly found that heating imines **1a–c** with cyclopentadiene above 80 °C results in previously unknown isomeric C-amidoalkylated cyclopentadiene derivatives **3a–c** and **3′a–c**. To the best of our knowledge, such a direction of the reaction between imines and cyclopentadiene has not been documented.



Scheme 1 *Reagents and conditions:* i, trichloroethylene, 50 °C, 5 h; ii, PhMe, 55–60 °C, 8 h; iii, PhMe, MW (300 W), 80 °C, 2 h; iv, trichloroethylene, 80–90 °C, 5 h; v, $CHBr_3$, reflux, 72 h.

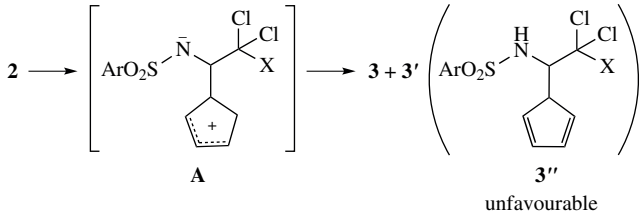
The method for the synthesis of dichloro(phenyl)acetaldehyde *N*-arylsulfonylimines **1d–f** is based on the addition of *N*,*N*-dichloroarenesulfonamides at phenylacetylene.[10] This procedure provides imines **1d–f** as individual compounds. Therefore, their further reaction with cyclopentadiene can be carried out in toluene, which is a 'classical' solvent for imine cycloaddition. In our experiments, imines **1d–f** reacted with cyclopentadiene at 55–60 °C in toluene for 8 h to afford the corresponding [4+2] cycloadducts, new azanorbornene derivatives **2d–f**, in high yields. Importantly, the reaction time for the synthesis of compounds **2d–f** can be reduced to 2 h by the use of microwave (MW) activation.

Both in the cases of chloral (**1a–c**) and dichloro(phenyl)-acetaldehyde (**1d–f**) imines, the cycloaddition proceeds selectively to give *exo*-isomers **2**. Apparently, this is due to a higher thermodynamic preference of *exo*-isomers as compared to *endo*-ones caused by steric factors. Nevertheless, minor quantities of *endo*-isomers were fixed by ^{1}H NMR in reaction mixtures in some cases.

The corresponding amidoalkylated derivatives of cyclopentadiene **3d**,**e**/**3′d**,**e** (X = Ph) are formed under much harsher reaction conditions than analogues **3a–c**/**3′a–c** (X = Cl), namely, boiling of cycloadducts **2d–e** in bromoform for 72 h is required.

A tentative route to the formation of amidoalkylated cyclopentadiene derivatives **3**/**3′** likely involves the initial cycloaddition to furnish [4+2] cycloadducts **2**. The latter upon heating would undergo the opening of the azanorbornene fragment (Scheme 2). Probably, this opening proceeds heterolytically across the N–C^{1}H bond to deliver bipolar intermediate **A**, which may exist in the form of several resonance structures. Further stabilization of intermediate **A** leads to the corresponding amidoalkyl-substituted cyclopentadienes **3**/**3′** existing in equilibrium in molar ratios close to 1 : 1. The third thermodynamically less preferable isomer **3″** was never detected both in the reaction mixtures and in the final products. Control experiments have confirmed that heating of cycloadducts **2** under the above reaction conditions [80–90 °C in trichloroethylene in the case of chloral derivatives **2a–c** or ~145–150 °C in bromoform in the case of dichloro(phenyl)acetaldehyde derivatives **2d**,**e**] really gave compounds **3**/**3′**. It should be noted that C-amidoalkylated derivatives **3a–c**/**3′a–c** can be also prepared byheating in toluene, DMF or DMSO.

The formation and structure of cycloadducts **2** and amidoalkylated derivatives of cyclopentadiene **3**/**3′** have been unambiguously confirmed by NMR and IR spectroscopy and elemental analysis. Their ^{1}H, ^{13}C, ^{15}N NMR spectra contain the proper signals for the characteristic protons, carbon and nitrogen atoms. The *exo*-configuration of 3-positioned substituent in adducts **2** is assigned using 2D NMR methods. Their NOESY spectra contain cross-peaks between 3- and 5-positioned protons of the cyclohexene moiety, which would correspond to the *exo*-location of polychloromethyl groups. In the NOE spectra of minor *endo*-isomer of **2b**, 3-positioned proton gives cross-peak with one of the protons of 7-CH_2 group. In ^{1}H NMR of **2b**, chemical shifts of H^3 protons are different for *exo*- (4.05 ppm) and *endo*- (4.88 ppm) isomers. Moreover, using 2D HSQC data we have measured the direct coupling constants $^1J_{C(3)H(3)}$ which differ for *exo*- and *endo*-derivatives because of stereospecific dependence on the nitrogen lone pair arrangement.[11] For *exo*- and *endo*-isomers of **2b**, the $^1J_{C(3)H(3)}$ values are 156.7 and 149.5 Hz, respectively. For the key NOE interactions, see Online Supplementary Materials (Figure S1).



Scheme 2

For isomeric amidoalkylated cyclopentadienes **3**/**3′**, the NOE effect occurred involving NH protons and cyclopentadienyl ones located in the positions 2 and 5 (for isomers **3**) and in the positions 1 and 3 (for isomers **3′**), which corresponds to 1- or 2-substituted cyclopentadienyl derivatives, respectively.

In summary, dichloro(phenyl)acetaldehyde *N*-arylsulfonylimines were explored for the first time in cycloaddition with cyclopentadiene, which gave new functional derivatives of 2-azabicyclo[2.2.1]hept-5-enes. A possibility for synthesis of amidoalkylated cyclopentadiene derivatives by reaction with polychloroacetaldehyde *N*-arylsulfonylimines was demonstrated.

The main results were obtained using the equipment of Baikal Analytical Center of Collective Using, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.022.

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