ALKYLATION OF CYMANTRENE WITH 1-BROMOADAMANTANE INITIATED BY IRON PENTACARBONYL

Cite this: *INEOS OPEN*, **2019**, *2 (1)*, 29–32
DOI: 10.32931/io1905a

Received 24 May 2018,
Accepted 10 November 2018

http://ineosopen.org

T. T. Vasil'eva, H. H. Hambardzumyan, N. E. Mysova, O. N. Gorunova, and K. A. Kochetkov*

Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow, 119991 Russia

Abstract

The reaction of cymantrene with 1-bromoadamantane is efficiently initiated by iron pentacarbonyl, affording a range of new alkyl and dialkyl-substituted products.

Key words: alkylcymantrenes, iron pentacarbonyl, alkylation with 1-bromoadamantane.

Introduction

The ability of iron pentacarbonyl to initiate a range of C–C bond forming reactions is well known [1–9]. Iron pentacarbonyl ($Fe(CO)_5$) was shown to promote the addition of α-halocarboxylic acid esters and nitriles to aldehydes and ketones by the Reformatsky-type reaction [1–3]. It was used successfully in diastereoselective hydrodimerization of aromatic aldehydes leading to diols [4], stereoselective reductive dimerization of chiral α-bromoamides resulting in bis(amides) [5], and addition of C_4F_9I to pentafluorobenzaldehyde [6] and benzyl bromide by the Zaitsev–Barbier reaction [7, 8].

Recently, in an attempt to accomplish the addition of 1-bromoadamantane to pentafluorobenzaldehyde by the Zaitsev–Barbier reaction in the presence of $Fe(CO)_5$ upon heating in aromatic solvents (benzene, toluene, chlorobenzene), we found that the desired reaction did not take place. Instead, the solvent, usually being inert under reaction conditions, underwent alkylation under action of the alkyl halide, which resulted in 1-aryladamantanes in high yields [9]. Thus, we revealed the ability of iron pentacarbonyl to initiate the Friedel–Crafts alkylation with 1-bromoadamantane. Later Khusnutdinov *et al.* suggested [10] other metal complexes as the catalysts for adamantylation of aromatic compounds. The possibility of alkylation of aromatic compounds with 1-bromoadamantane **I** under action of different Friedel–Crafts catalysts was shown earlier [11, 12], but metal carbonyls have not been used for this purpose. Furthermore, the reported examples required high temperatures, prolonged stirring, inert atmosphere, and, as a rule, high loadings (1–2 mol. eq) of the initiator to ensure the reaction completion and, in some cases, afforded lower yields of alkylation products. The reactions catalyzed by the Lewis acids often proceed under heterogeneous conditions [11, 12]. The use of iron or antimony chlorides leads to partial chlorination of adamantane [13]. Recent examples involve the use of rare reagents such as indium halides [14].

Sterically hindered reagent **I** was used in alkylation [11–14] and cross-couplings [15, 16] to introduce a bulky adamantyl moiety, which imparts specific physicochemical properties to products [17] and significantly changes their physiological activity [13, 18]. Nowadays, of particular interest is the development of antirabic vaccines based on aryl derivatives of adamantane [19]. Of note is also the antiproliferative activity of aminoadamantane [20].

Herein, we report on the initiating effect of $Fe(CO)_5$ on the alkylation of a representative of another class of aromatic compounds, namely, cymantrene **II** under action of alkyl bromide **I**. The alkylation of thermally unstable and light-sensitive aromatic organometallic compounds such as cymantrene **II** in the presence of acid catalysts proceeds nonselectively and is often accompanied by resinification [21, 22], therefore, it is usually accomplished by indirect routes via modification of other derivatives [23].

Results and discussion

The reaction of 1-bromoadamantane **I** with cymantrene **II** in cyclohexane in the presence of $Fe(CO)_5$ (2 mol. eq) upon heating at 80 °C resulted in the high conversion of the reagents already over 2 h and, depending on the ratio of reagents, afforded a mixture of new products of mono- and dialkylation of cymantrene, adamantylcymantrene **III** and 1,3-diadamantylcymantrene **IV**, with domination of one of them along with the small amount of 1-(3-bromoadamantyl)-3-adamantylcymantrene **V**. In the absence of $Fe(CO)_5$, the reaction did not take place. Furthermore, the reaction result strongly depended on the solvent in use. Thus, the application of dichloromethane and dichlorobenzene led to trace amounts of the products of chlorination of compounds **III** and **IV**, which were identified using mass spectrometry. The use of $Fe(CO)_5$ as a solvent, reported earlier in the literature [24], in this case led to a decrease in the product yields. Compounds **III**–**V** were isolated by preparative TLC on silica gel.

According to the NMR spectroscopic data, the main reaction product at 1:1 ratio of the reagents was adamantylcymantrene **III**, which was obtained in 50% yield, whereas the minor product, 1,3-diadamantylcymantrene **IV**, was formed in <5% yield. A double excess of bromoadamantane relative to cymantrene afforded, along with monoalkylation product **III** (16%) and main dialkylation product **IV** (42%), 1-(3-bromoadamantyl)-3-adamantylcymantrene **V** (15%), which was likely to result from the bromination of compound **IV**. The mass spectrometric analysis of the final product mixture revealed trace amounts of another bromination product, monobromoadamantylcymantrene **VI**, and the product of hydrolysis of starting compound **II**, adamantyl alcohol **VII**.

The structures of products **III**–**V** (Scheme 1) were supported by the IR and NMR spectroscopic as well as mass spectrometric data. The structures of compounds **IV**, **V** were also elucidated by single-crystal XRD (for preliminary crystallographic data, see Electronic Supplementary Information).

The plausible mechanism of alkylation includes the formation of an intermediate complex of $Fe(CO)_5$ with bromoadamantane that activates alkyl halide [25] and gives rise to a radical, as it was assumed earlier [6–8]. The reaction conditions explored are likely to facilitate the formation of a sterically hindered radical or radical ion [26, 27]. Subsequent processes comprise the alkylation of the aromatic ring or intermediate addition at the central atom of cymantrene, as it was supposed earlier for other species [23], followed by alkylation by the ricochet mechanism [28]. The second substitution with the adamantyl fragment occurs at the third position of the ring due steric hindrances. The radical mechanism of cymantrene alkylation is also supported by the formation of bromo derivatives **V** and **VI** as a result of substitution at the tertiary carbon atom of the adamantyl moiety and the formation of products of partial chlorination of compounds **III** and **IV** in the reactions in dichloromethane and dichlorobenzene.

Experimental

General remarks

The ^{1}H NMR spectra were registered on a Bruker WP-400 spectrometer (400 MHz) using $CDCl_3$ as a solvent. The chemical shifts are presented relative to tetramethylsilane. The IR spectra were recorded on a UR-20 spectrometer. The mass spectra were obtained on a Finigan SSQ-7000 mass spectrometer with the direct injection of samples and the ionizing voltage of 70 eV. The XRD experiments were carried out with a SMART 1000 CCD diffractometer (Mo Kα radiation, graphite monochromator, ω-scanning) at 120 K.

The reaction course was monitored by TLC on aluminum plates with 60 F_{254} neutral aluminum oxide carrier of Merck production in petroleum ether (40–70 °C)–ethyl acetate (10:1). The reaction products were isolated from the reaction mixture using preparative thin-layer chromatography on glass plates with 60 PF_{254} silica gel containing 30% of gypsum (Merck). Bromoadamantane was purchased from Aldrich. $Fe(CO)_5$ was purchased from Fluka (98%) and used without further purification.

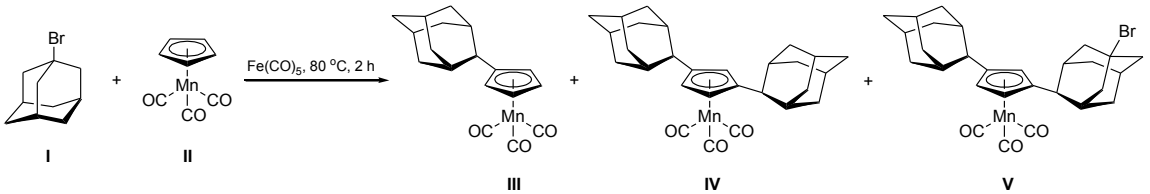
Syntheses

Alkylation of cymantrene with 1-bromoadamantane in the presence of iron pentacarbonyl (1:2 ratio).

A double-neck flask equipped with a condenser, stirrer, and Tishchenko bottle was charged with a mixture of cymantrene **II** (0.246 g, 1 mmol) and bromoadamantane **I** (0.459 g, 2 mmol) in cyclohexane (2 mL) under vigorous stirring. Then $Fe(CO)_5$ (0.27 mL, 2 mmol) was added. After dissolution of the components (10–15 min), the reaction mixture was stirred upon heating at 80 °C for 5 h. The reaction can be promoted by addition of a drop of ~1% solution of $CBrCl_3$ in cyclohexane as an activator. No evolution of CO was detected. The reaction mixture was evaporated and extracted with 10 mL of benzene. The resulting residue was treated with 30 mL of 1 N aq. HCl and additionally extracted with benzene. The combined benzene fractions were washed with water (×3) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue obtained (0.454 g) was washed with methanol (2×5 mL) and decanted (the mass of the dry residue comprised 0.152 g). Then the methanol solution was evaporated to give 0.270 g of a mixture of compounds **III**–**VI**. The products were separated by preparative TLC on silica gel (eluent: petroleum ether), which afforded three fractions. The first fraction contained the product of hydrolysis of **I** (0.092 g) (<1 %), according to the mass spectrometric data, adamantyl alcohol **VII**. The second fraction (0.062 g) comprised initial cymantrene **II** (75% conversion). According to the NMR spectroscopic data, the third fraction (0.120 g) involved a mixture of 1,3-diadamantylcymantrene **IV** (23%, calculated per unreacted compound **II**) and adamantylcymantrene **III** (16%, calculated per unreacted compound **II**) in 2:1 ratio. The latter (0.153 g) was dissolved in $CHCl_3$ and additionally purified by preparative TLC on silica gel (eluent: petroleum ether) to give two products. The first product (0.063 g, 15%, calculated per unreacted compound **II**) represented bromodiadamantylcymantrene **V** bearing trace amounts of bromoadamantylcymantrene **VI**, and the second product (0.066 g, 19%, calculated per unreacted product **II**) was 1,3-diadamantylcymantrene **IV**.

Alkylation of cymantrene with 1-bromoadamantane in the presence of iron pentacarbonyl (1:1 ratio).

The reaction was carried out upon stirring of a mixture of cymantrene **II** (0.271 g, 1.1 mmol), bromoadamantane **I** (0.253 g, 1.1 mmol), $Fe(CO)_5$ (0.30 mL, (2.2 mmol), and cyclohexane



Scheme 1. Alkylation of cymantrene with 1-bromoadamantane.

(2 mL) at 80 °C for 4 h. The conversion of **II** composed 70%. The isolation of adamantylcymantrene **III** was carried out analogously to the above example from the methanol extract (0.132 g, 50%, calculated per unreacted compound **II**).

Adamantylcymantrene, III. ^{1}H NMR (δ, ppm): 1.77 (m, 12H), 2.07 (m, 3H), 4.62 (m, 2H), 4.90 (m, 2H). MS, *m/z* (I_{rel}, %): 338 $[M]^{+\bullet}$ (13), 282 $[M–2CO]^{+\bullet}$ (10), 272 $[M–66]^{+\bullet}$ (23), 254 $[M–3CO]^{+\bullet}$ (100), 252 (26), 199 $[M–3CO–Mn]^+$ (18). Anal. Calcd for $C_{18}H_{24}MnO_3$: C, 63.52; H, 7.32. Found: C, 62.97; H, 7.05%.

1,3-Diadamantylcymantrene, IV. ^{1}H NMR (δ, ppm): 1.75 (m, 18H), 2.08 (m, 4H), 2.30 (8H), 4.63 (м, 2H), 4.88 (s, 1H). IR (KBr, ν/cm^{-1}): 2907, 2850 (C–Ad), 2001, 1928, 1909 (C=O). MS, *m/z* (I_{rel}, %): 472 $[M]^{+\bullet}$ (3), 406 $[M–66]^{+\bullet}$ (32), 388 $[M–3CO]^{+\bullet}$ (100), 333 (13), 135 $[Ad]^+$ (28).

1-(3-Bromoadamantyl)-3adamantylcymantrene, V. MS, *m/z* (I_{rel}, %): 550/552 $[M]^{+\bullet}$ (3/3), 484/486 $[M–66]^{+\bullet}$ (23/23), 466/468 $[M–3CO]^{+\bullet}$ (17/17), 400 (10), 386 $[M–3CO–HBr]^{+\bullet}$ (20), 135 $[Ad]^+$ (100).

Bromoadamantylcymantrene, VI. MS, *m/z* (I_{rel}, %): 416/418 $[M]^{+\bullet}$ (6/6), 360/362 $[M–2CO]^{+\bullet}$ (18/18), 350/352 $[M–66]^{+\bullet}$ (31/28), 332/334 $[M–3CO]^{+\bullet}$ (100/90), 290/292 (15/16), 276/278 (55/53), 252 $[M–3CO–HBr]^{+\bullet}$ (82), 196 $[C_{15}H_{16}]^{+\bullet}$ (97), 141 (47), 128 (28), 115 (34), 93 $[C_7H_9]^+$ (63), 91$[C_7H_7]^+$ (43), 79 $[C_6H_7]^+$ (12), 77 $[C_6H_5]^+$ (20), 55 $[Mn]^+$ (25).

The structures of crystalline products **IV**–**V** were elucidated by XRD. The mass spectrum of adamantyl alcohol **VII** completely coincided with the previously published data [29].

Conclusions

Hence, we succeeded in efficient initiation of cymantrene alkylation with 1-bromoadamantane under action of iron pentacarbonyl, which led to a range of new mono- and disubstituted products. Unlike the previously reported example of alkylation of aromatic compounds with bulky adamantyl fragment [10], in our case the relative content of dialkylated products were high. This example open new opportunities for the application of iron pentacarbonyl as an initiator for different C–C bond forming reactions involving not only aliphatic [1–8] and aromatic [9] derivatives, but also organometallic compounds.

Acknowledgements

This work was carried out in the framework of the state assignment for INEOS RAS.

The authors are grateful to the contribution of Center for molecular composition studies of INEOS RAS.

Corresponding Author

* E-mail: const@ineos.ac.ru (K. A. Kochetkov)

Electronic supplementary information

Electronic supplementary information (ESI) available online: preliminary X-ray crystallographic data for compounds **IV** and **V**

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