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Graphical Abstract

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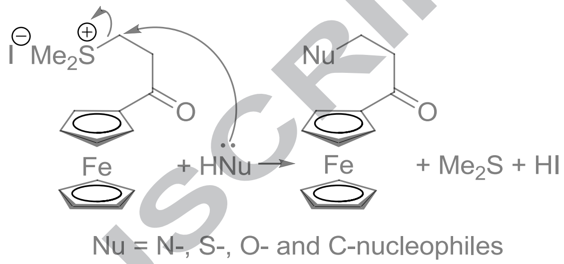
The title salt was synthesized and submitted to reaction with several N-, S-, and O-nucleophiles (to give the corresponding β-functionalized 1-ferrocenylpropan-1-ones), as well as with C-nucleophiles (to give products containing a new C-C bond).



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[b] *Technical Faculty Kosovska Mitrovica,University of Priština, Kneza Miloša 7, 38220 Kosovska Mitrovica, Serbia*
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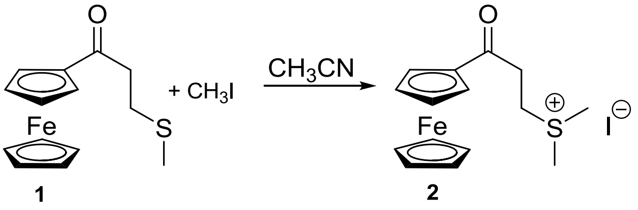
ABSTRACT

Dimethyl(2-ferrocenoylethyl)sulfonium iodide was synthesized by reacting 1-ferrocenyl-4-thiapentan-1-one with iodomethane and characterized from spectral data and single crystal X-ray structure analysis. This compound was capable of reacting with different N-, S- and O-nucleophiles giving the corresponding β-functionalized ferrocene-containing ketones. Furthermore, dimethyl sulfide can be displaced from the dimethyl(2-ferrocenoylethyl)sulfonium ion with cyanide or carbanions derived from 1,3-bifunctional compounds and nitropropane, leading to products with a new carbon-carbon bond.

Since its discovery more than sixty years ago, ferrocene has acquired significant attention as a consequence of its unique physical and chemical properties which allow for its application in many fields of science, ranging from materials science and asymmetric catalysis to analytical chemistry and medicine (bioorganometallic chemistry).[1] Thus, despite the general opinion that organometallic compounds are extremely sensitive to moisture, ferrocene does not react with water and can be handled in air when solid and often in solution. On the other hand, ferrocene can be easily functionalized, Friedel-Crafts acylation being the most frequently used.[2] The carbonyl group of acylferrocenes obtained in this way provides a plethora of possibilities for further transformations, utilizing classical methods of organic chemistry. Acylation is a particularly suitable method for the derivatization of ferrocene which allows for simultaneous introduction of an additional heteroatom into the newly synthesized acylferrocene. Employing a modified Friedel-Crafts acylation of ferrocene,[3] we reported on the synthesis of several acylferrocenes containing sulfur in their alkyl chains.[4] The synthetic value of these compounds has been recognized in the synthesis of highly functionalized ferrocene-containing cyclopropane derivatives using 1-ferrocenyl-3-thiabutan-1-one via the corresponding sulfonium salt, i.e. via a stabilized sulfur ylide.[5] In the present communication, we outline the first results on the synthetic applications of 1-ferrocenyl-4-thiapentan-1-one (**1**), based on a formal substitution of the methylthio group with several nucleophiles.

The utilization of 1-ferrocenyl-4-thiapentan-1-one (**1**) in organic synthesis has been conceptualized as the transformation of the methylthio group into a good leaving group $[-S^{\oplus}(CH_3)_2]$, by reacting this β-(methylthio)ketone with iodomethane (Scheme 1) and further substitution of this group with nucleophiles. An acetonitrile solution of ketone **1** and twice the amount of iodomethane was stirred at room temperature, while a yellow precipitate formed. On the basis of spectral data (IR, ^{1}H and ^{13}C NMR) this product was identified as dimethyl(2-ferrocenoylethyl)sulfonium iodide (**2**). Recrystallization of the crude product from methanol gave brass-yellow crystals of **2**, which were in the shape of very thin plates with a thickness of less than 0.01 mm and, therefore, not fully suitable for single-crystal X-ray structure analysis. Nevertheless X-ray analysis



Scheme 1. Synthesis of salt **2**

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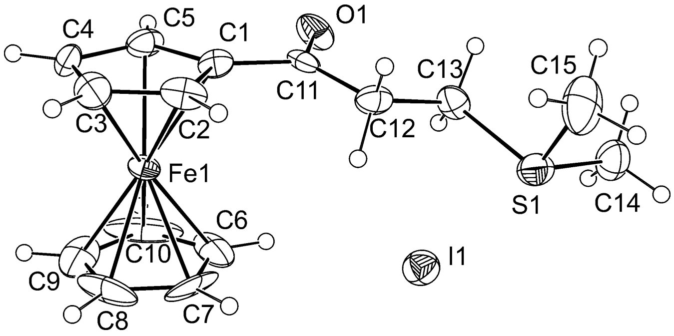
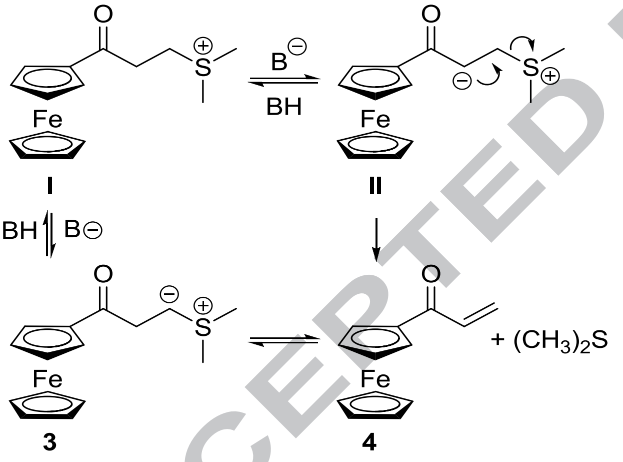


Figure 1. ORTEP drawing of the molecular structure of compound **2**. Displacement ellipsoids are drawn at the 40% probability level.[6]

successfully and unambiguously confirmed the structure of **2** (Figure 1).

Salt **2** was submitted to reaction with sodium hydride in benzene. In contrast to the salt obtained from 1-ferrocenyl-3-thiabutan-1-one,[5] compound **2** did not give the corresponding ylide (**3**, Scheme 2). Instead, we isolated acryloylferrocene (**4**, Scheme 2) in quantitative yield. A reversible deprotonation of the dimethyl(2-ferrocenoylethyl)sulfonium cation (**I**, Scheme 2) is, certainly, possible at both, the α-sulfonium and α-keto positions, but the product obtained through the second process (dipolar ion **II**, Scheme 2) undergoes irreversible elimination, giving ketone **4** as the sole product. The same product was obtained by treating **2** with a water solution of sodium hydroxide, as was also reported for an analogue of salt **2,** dimethyl(2-benzoylethyl)sulfonium bromide containing a phenyl group instead of a ferrocene.[7]

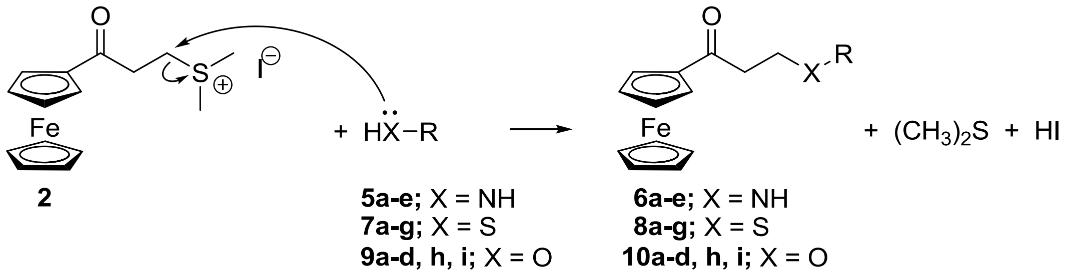


Scheme 2. Reaction of salt **2** with bases

To investigate substitution reactions of salt **2**, it was submitted to reactions with several nucleophiles. Thus, when **2** was refluxed with two equivalents of aniline in methanol, the corresponding β-(phenylamino)ketone **6a** (Scheme 3) was obtained in a 75% yield. The generality of this reaction was evaluated using four additional anilines as nucleophiles (**5b-e**) and, as shown in Scheme 3 and Table 1, the corresponding Mannich bases **6b-e** were obtained in moderate to very high yields.

Salt **2** was next treated with thiophenol (**7a**) under the same conditions (in refluxing methanol). The expected ketosulfide was not obtained, but instead the corresponding methoxy derivative **10h** (Scheme 3), in a low yield (up to 20%). The remainder of salt **2** was converted into ketone **1**. In order to find optimum conditions that might provide an approach to ketosulfides different (but less available) from ketone **1** utilizing this methodology, we tested several solvents (with or without a base) as the reaction medium. It was found that **2** reacted with thiophenol in ethyl acetate in the presence of potassium carbonate giving the corresponding ketosulfide **8a** (Scheme 3) in a 78% yield. Four additional thiophenols (**8b-e**), as well as two aliphatic mercapto derivatives, esters **7f**, and **7g**, were also used as nucleophiles with the same success (see Scheme 3 and Table 1). However, some amounts of ketone **1** (up to 20%) were always obtained as side products in these reactions (for details see the Supporting Information).

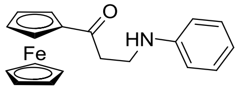
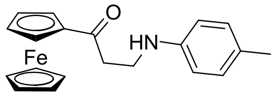
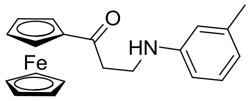
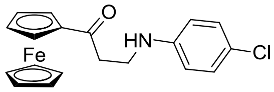
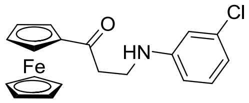
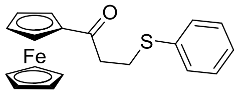
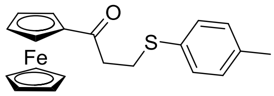
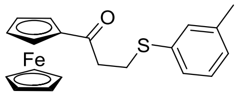
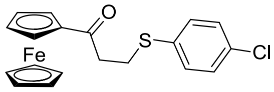
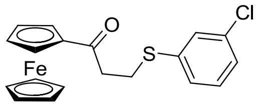
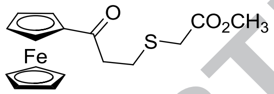
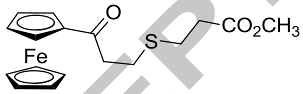
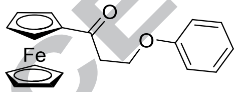
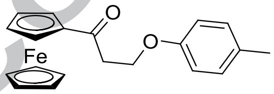
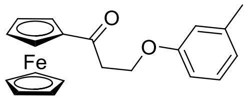
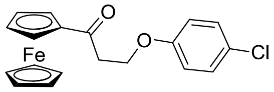
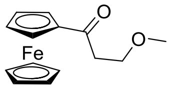
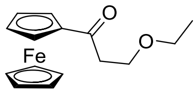
Many efforts were made to optimize the substitution of dimethylsulfide from salt **2** with the phenoxy group, but a solvent suitable for the successful synthesis of 1-ferrocenyl-3-phenyloxypropan-1-one (**10a**) was not found. Treatment of **2** with phenol in methanol, acetonitrile, DMF, DMSO and ethyl acetate gave either acryloylferrocene (in the presence of a base) or ketone **1** (without the base). The synthesis of this ether was achieved by exposing a solid mixture of salt **2** and phenol **9a** to ultrasound irradiation. However, ether **10a** was obtained in a low yield (35%), whereas the main product of this reaction was acryloylferrocene (**4**; 60%; see the Supporting Information). Three additional phenols (**9b-d**) were used as substrates under the same conditions giving the corresponding β-aminoketones in similar yields (**10b-d**; up to 42%; see Scheme 3 and Table 1). On the other hand, on refluxing **2** in methanol and ethanol in the presence of sodium hydroxide, the corresponding methoxy- and ethoxyketones (**10h**, and **10i**, Scheme 3) were obtained in almost quantitative yields (Table 1).



R: **a)** C_6H_5, **b)** *p*-$CH_3C_6H_4$, **c)** *m*-$CH_3C_6H_4$, **d)** *p*-ClC_6H_4, **e)** *m*-ClC_6H_4, **f)** $CH_2CO_2CH_3$,
g) $CH_2CH_2CO_2CH_3$, h) CH_3, **i)** C_2H_5

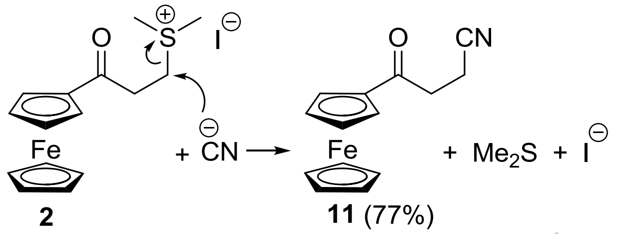
Scheme 3. Reaction of salt **2** with N-, S- and O-nucleophiles

Table 1. Reactions of salt **2** with N-, S- and O-nucleophiles[a]

Entry	Nucleophile	Product		Yield (%)[b]
1	**5a**		**6a**	75
2	**5b**		**6b**	88
3	**5c**		**6c**	98
4	**5d**		**6d**	63
5	**5e**		**6e**	45
6	**7a**		**8a**	78
7	**7b**		**8b**	87
8	**7c**		**8c**	84
9	**7d**		**8d**	84
10	**7e**		**8e**	80
11	**7f**		**8f**	78
12	**7g**		**8g**	98
13	**9a**		**10a**	35
14	**9b**		**10b**	31
15	**9c**		**10c**	42
16	**9d**		**10d**	32
17	**9h**		**10h**	90
18	**9i**		**10i**	98

[a] For experimental details and spectral data of the new compounds see the Supporting Information.

[b] Isolated yields based on salt **2**.



Scheme 4. Reaction of salt **2** with cyanide

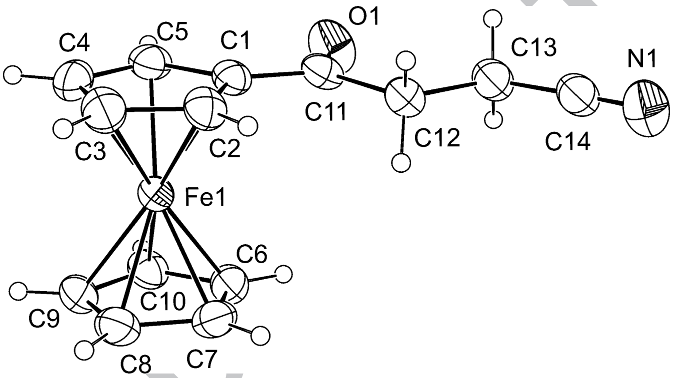
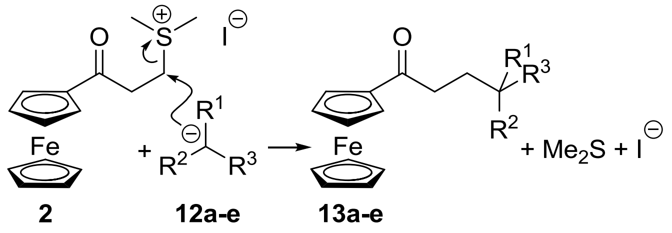
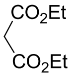
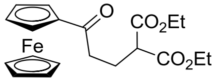
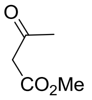
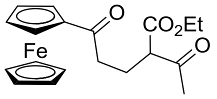
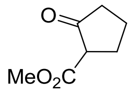
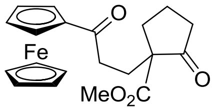
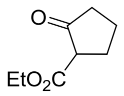
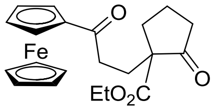
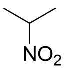
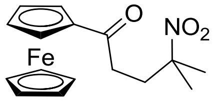


Figure 2. ORTEP drawing of the molecular structure of compound **11**. Displacement ellipsoids are drawn at the 40% probability level.[8]

Finally, we decided to examine the possibility of using salt **2** for the formation of a new carbon-carbon bond. This salt reacted smoothly with potassium cyanide in water giving 4-ferrocenyl-4-oxobutanenitrile (**11**) in 77% yield (Scheme 4). The molecular structure of this compound was also confirmed by X-ray diffraction (Figure 2).

Table 2. Reactions of salt **2** with some C-nucleophiles[a]



Entry	Nucleophile		Product		Yield (%)[b]
1		**12a**		**13a**	71
2		**12b**		**13b**	57
3		**12c**		**13c**	85
4		**12d**		**13d**	81
5		**12e**		**13e**	50

[a] For experimental details and spectral data of the new compounds see the Supporting Information.

[b] Isolated yields based on salt **2**.

Examinations aimed at utilizing **2** in the alkylation of 1,3-bifunctional carbonyl compounds[9] were begun by the reaction of this salt with the carbanion generated from diethyl malonate **12a** (Table 2) in tetrahydrofuran, whereby the corresponding product **13a** was obtained in 71% yield. In order to evaluate the generality of this reaction, three additional anions obtained from 1,3-bifunctional carbonyl compounds **12b-d** as well as from 2-nitropropane (**12e**), were submitted to the same reaction conditions. As depicted in Table 2, these substrates reacted to give the corresponding 5-ferrocenyl-5-oxo-2-substituted carboxylates **13b-d**, and 1-ferrocenyl-4-methyl-4-nitropentan-1-one (**13e**) in moderate to high yields.

In conclusion, we have presented new and useful synthetic manipulations of dimethyl(2-ferrocenoylethyl)sulfonium iodide (**2**) as a donor of a 3-ferrocenyl-3-oxopropyl group in the synthesis of amines, organic sulfides and ethers containing this group. In addition, we showed that this salt can be used as an alkylating agent in the synthesis of 5-ferrocenyl-5-oxo-2-substituted carboxylates from the corresponding 1,3-dicarbonyl compounds. The products of these reactions represent useful multifunctional ferrocene derivatives that can serve as starting materials for the synthesis of more complex derivatives of this metallocene.

Acknowledgements

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Supplementary data

Supplementary data (complete experimental procedures, IR and NMR spectra of the new compounds and comments on the X-ray structural analyses of compounds **2** and **11**) associated with this article can be found in the online version, at

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6. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 934348 for compound **2**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information.
7. B hme, H.; Heller, P. *Chem. Ber.* **1953**, *86*, 443-450.
8. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 934349 for compound **11**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information.
9. To the best of our knowledge, only one literature report on the use of an analogous ketosulfonium system (4-oxohexahydrothiopyrylium iodide) in the alkylation of 1,3-dicarbonyl compounds has appeared up to present. See: Cardwell H. M. E. *J. Chem. Soc.* **1949**, 715-719.