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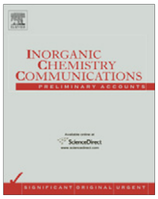

Microwave assisted synthesis of ferrocene amides

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A R T I C L E I N F O

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ABSTRACT

A new microwave assisted synthesis methodology has been presented for the preparation of the ferrocene amides. Ferrocene carboxylic acid was derivatised using direct 1*H*-Benzotriazole/$SOCl_2$ methodolgy to prepare *N*-ferrocenoyl benzotriazole as a new starting material for the functionalization of ferrocene ring. *N*-ferrocenoyl benzotriazole was reacted with mono- and di-amines under microwave irradiation to prepare ferrocene mono- and di-amides in high purity and in good yield.

Ferrocene derivatives have widespread applications in chemistry. Because of the redox potential of the ferrocene, different type of ferrocene containing organics were prepared and used in several applications [1a–g]. On the other hand, some ligands and complexes including ferrocene moiety were prepared for the inorganic applications [2a–d]. Ferrocenoyl amino acids and peptides were prepared using acyl ferrocenes and investigated detailed in literature [3a–d].

Ferrocene amides have been prepared by amide formation between amines and ferrocenecarboxylic acid derivatives. In these methods ferrocene carboxylic acid was activated by transforming into; the acid chloride [4] succinimid [5], 1-hydroxybenzotriazole ester in presence of DCC or EDC [5] or insitu activation of carboxylic acid by HBTU or TBTU [6]. Acid fluoride of ferrocene carboxylic acid was prepared for the derivatisation of ferrocenoyl group using cyanuric fluoride [7]. As an alternative to the above methods, we used 1*H*-Benzotriazole/$SOCl_2$ methodology for the preparation of novel *N*-Ferrocenoyl benzotriazole as starting material for the derivatisation of ferrocenoyl group. Althought this method was used for the preparation of different kind of *N*-Acyl benzotriazoles [8], it was not used for the preparation of *N*-Ferrocenoyl benzotriazole. This compound is a novel, reddish crystaline, easy to handle and reactive towards the amines. Additionally preparation of this compound do not needs special catalyst like DCC or EDC as in HOBt method.

On the other hand, different from the literature, in this work we prepared ferrocene amides by microwave irradiation. Microwave synthesis has growing interest in the field of synthetic organic chemistry. The theory and the effect of microwaves in organic synthesis were fully described by Oliver Cape [9]. *N*-acylation of several type of amines using microwave irradiation was conducted in literature and these affords were reviewed by Pelle Lindström and co-workers [10]. Parallel synthesis of amide library based on the 6,8-dioxa-3-azabicyclo[3.2.1]-octane scaffold using microwave irradiation is reported by Fabrizio Machetti and co-workers [11]. β-lactams containing the ferrocene moiety has been synthesized by a one-pot reaction of ferrocenyl acetic acid and achiral or chiral imines with both the conventional thermal methods and the more rapid microwave irradiation technique [12]. Ferrocene containing fulleren derivatives were prepared using microwave heating [13]. According to our knowledge this is the first example of microwave assisted synthesis of the ferrocene amides using *N*-Ferrocenoyl benzotriazole.

Starting material **1** was prepared by the reaction of ferrocenecarboxylic acid and 1*H*-benzotriazole in presence of thionylchloride similar to published procedure [8] (Scheme 1).

^1H NMR spectra of **1** shows characteristic signals of *N*-substitued benzotriazole between 7.5 and 8.5 ppm and characteristic signals of mono-substitued ferrocene around 4.0–5.5 ppm. Moreover, ^{13}C NMR spectra of **1** supports formation of this structure via mono-substitued ferrocene peaks around 69–74 ppm and *N*-substitued benzotriazole peaks between 110 and 148 ppm.

Starting material was treated with an equimolar amount of amine (in case of di-amines 2 equivalent of starting material **1** was used) in $CHCl_3$ refluxing at 82 °C using 90 W MW irradiation for 30 min. to give the corresponding amides [14] **2a–j** and **3a–d**.

The ^1H NMR spectra of these products show no signals corresponding to these assigned to the *N*-substitued benzotriazole groups of starting material **1** (between 7.5 and 8.5 ppm two dublet and two triplet.). The ^{13}C NMR spectra of these compounds also no longer show signals for a *N*-substitued benzotriazole group (Chemical shifts around 120 ppm and 146 ppm). Products show characteristic ferrocene peaks around 4.0–5.0 ppm in ^1H NMR and

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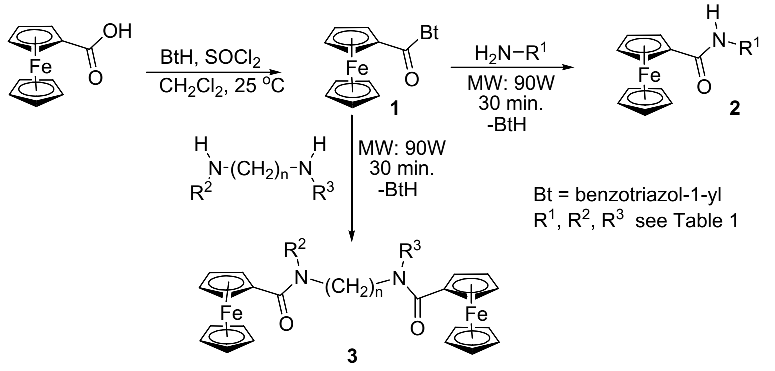


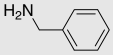
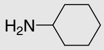
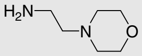
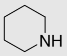
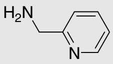
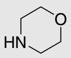
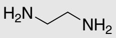
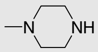
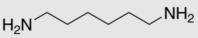
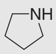
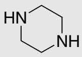
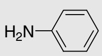
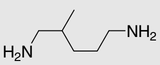
Scheme 1. Preparation of ferrocene mono- and di-amides.

69–75 ppm in ^{13}C NMR. Products **2a–b**, **2g–j** and **3a–d** shows signals around 5.50–6.50 ppm corresponding to N–H bond of amide (cyclic amines, which have nitrogen atom in ring, does not show this signal). No significant shift was observed for the carbonyl carbon (around 170 ppm) during the transformation from starting material **1** to products **2a–j** and **3a–d**. In general ^{1}H NMR signals were broad and couplings are not visible for some products because of the possible paramagnetic impurities and the conformational changes in these molecules.

Since ferrocene ring contains metal, this compound is assigned as a highly microwave absorbent compound. Thus $CHCl_3$, which has low dielectric loss (0.437) and loss tangent ($\tan\delta = 0.091$) [15] value, was chosen as a microwave transparent solvent to prevent over heating and hot spots as much as possible.

Preparation of **2b** was carried out with microwave irradiation and conventional methods separately (reaction at room temperature and refluxing in $CHCl_3$) to determine the microwave effect on the preparation of investigated ferrocene amides. Cyclohexylamine and **1** were stirred in $CHCl_3$ at room temperature under nitrogen atmosphere for 4 h and during this period no reaction was observed according to TLC analysis. Then reaction mixture was refluxed for 3 days period and desired product **2b** was

Table 1
Amines for the preparation of ferrocene amides

Entry	Product	Amine	Yield %	Entry	Product	Amine	Yield %
1	**2a**	NH_4OH	52	8	**2h**	 benzylamine	64
2	**2b**	 cyclohexylamine	81(54)[a]	9	**2i**	 4-(2-aminoethyl)morpholine	71
3	**2c**	 piperidine	92	10	**2j**	 2-picolylamin	93
4	**2d**	 morpholine	87	11	**3a**	 Ethylenediamine	95
5	**2e**	 1-methylpiperazine	63	12	**3b**	 1,6-diaminohexane	54
6	**2f**	 pyrrolidine	91	13	**3c**	 piperazine	65
7	**2g**	 aniline	61	14	**3d**	 2-Methyl-1,5-pentanediamine	62

[a] Isolated yield after refluxing 3 days in $CHCl_3$.

observed in %54 yield after purification. Consequently, we can say that microwave has advantages on reaction time and the product yield on these type of reactions (see Table 1).

In this work we presented a new starting material for the activation of ferrocene carboxylic acid and a new, easy and fast synthetic approach for the synthesis of ferrocene amides in good to excellent yield using microwave assisted organic synthesis.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2008.05.023.

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