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Synthesis of novel ferrocene-containing 1,3-thiazinan-2-imines: one-pot reaction promoted by ultrasound irradiation

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ABSTRACT

A simple one-pot synthesis of new ferrocene-containing 1,3-thiazinan-2-imines from 3-arylamino-1-ferrocenylpropan-1-ols and phenyl isothiocyanate has been developed. The key intermediate β-hydroxy thioureas were generated *in situ* using ultrasound irradiation and subsequent cyclization was achieved by the addition of acetic acid. The scope of the reaction towards various 3-arylamino-1-ferrocenylpropan-1-ols has been explored and the corresponding 3-aryl-6-ferrocenyl-*N*-phenyl-1,3-thiazinan-2-imines were obtained in moderate to high yields (52-90%).

Since its discovery in 1951,[1] ferrocene and its derivatives have found applications in many areas, among which the most important are materials science, asymmetric catalysis, bioorganometallic chemistry, and organic synthesis.[2] Due to their unique properties, such as thermal and hydrolytic stability, and the presence of a reversible redox Fe^{2+}/Fe^{3+} center, the ferrocene unit has been recognized as an attractive pharmacophore in drug design.[3] Incorporation of this moiety into biologically relevant molecules, such as heterocyclic compounds, represents a popular approach for the synthesis of medicinally promising compounds. Among heterocycles, the 1,3-thiazine framework represents an important structural motif which is present in natural products and bioactive compounds with diverse activities,[4] such as antimicrobial,[5] antitumor,[6] antioxidant,[7] calcium channel modulator,[8] and antipyretic.[5, 9] Consequently, there is significant interest in the development of new synthetic methodologies for the construction of this heterocyclic ring.

As part of our ongoing project oriented toward the development of new methods for the synthesis of potentially bioactive ferrocene-containing heterocyclic compounds,[10, 11] we recently reported the synthesis of several classes of ferrocene-containing heterocyclic compounds.[12, 13] 3-Arylamino-1-ferrocenylpropan-1-ols were recognized as useful intermediates in the syntheses of diverse ferrocene heterocycles.[11, 12] Starting from these 1,3-aminoalcohols, ferrocene derivatives of six-membered cyclic ureas,[11] tetrahydroquinolines,[12] and quinolines[12] were synthesized (Scheme 1, previous work). Therefore, we considered employing them in the reaction with phenyl isothiocyanate, expecting, by analogy with our previous work, to obtain the corresponding β-hydroxy thioureas. Further cyclization of these intermediates would then provide either *N*- and/or *S*-alkylated heterocycles (Scheme 1, this work). Therefore, in the present work, we report the chemoselective synthesis of ferrocene-containing 1,3-thiazinan-2-imines – 3-aryl-6-ferrocenyl-*N*-phenyl-1,3-thiazinan-2-imines (**7a-n**) *via* the reaction between 3-arylamino-1-ferrocenylpropan-1-ols and phenyl isothiocyanate. To the best of our knowledge, there are no reported examples of ferrocene-containing 1,3-thiazinan-2-imines in the literature.

Based on our previous work we postulated that the previously optimized conditions[11, 14] might be applicable for this synthetic pathway. Therefore, 1,3-aminoalcohol **1a** (1 mmol) was reacted with phenyl isothiocyanate (1.2 mmol), in the absence of solvent and catalyst. The reaction mixture was irradiated for 2 h in an ultrasound bath at ambient temperature and the reaction was monitored by TLC. Then, the crude product was purified by

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