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Synthesis of ferrocene-containing six-membered cyclic ureas *via* α-ferrocenyl carbocations†

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A series of ferrocene-containing six-membered cyclic ureas (1-aryl-4-ferrocenyl-3-phenyltetrahydropyrimidin-2(1*H*)-ones) was synthesized (in high-to-excellent yields) by reacting the corresponding amino-propanols with phenyl isocyanate and the subsequent intramolecular cyclization of the thus obtained β-hydroxy ureas (prompted by acetic acid), *via* an α-ferrocenyl carbocation.

Six-membered cyclic ureas make up the core structure of a number of molecules possessing interesting biological features (Fig. 1), such as action on the central nervous system (**1**),[1] retinoidal (**2**)[2] and herbicidal (**3**)[3] activities, as well as dihydroorotase (**4**)[4] and HIV protease (**5**)[5] inhibiting activities. Furthermore, while some readily accessible and re-isolable representatives of five-membered cyclic ureas were used as efficient chiral auxiliaries in asymmetric organic synthesis,[6] a six-membered urea, 3-decyl-4-hydroxymethyltetrahydropyrimidin-2-one, was exploited in the chiral resolution of some polyfunctional xanthone derivatives.[7] Therefore, considerable interest exists among synthetic and medicinal chemists in the development of this class of compounds, and a multitude of reports dealing with these compounds appeared in the literature.

As extensively summarized ten years ago,[8] most of the reported methods for the synthesis of cyclic ureas refer to the oldest method based on the reaction of diamines with carbonic acid derivatives (phosgene chiefly, but also urea and dialkyl carbonates), carbon monoxide and carbon dioxide; recently published protocols mainly represent (improved) variants of earlier ones (see, for example, ref. 9).

In continuation of our permanent interest in the synthesis of ferrocene derivatives, particularly those that are potentially bioactive, we decided to synthesize a series of new ferrocene-containing six-membered cyclic ureas (tetrahydropyrimidin-2-ones). The following two main motives stimulated us to undertake this project: (i) a general notion exists that increased lipophilicity of cyclic ureas enhances their biological activity (incorporation of a ferrocene unit into organic molecules, such as six-membered cyclic ureas, will certainly cause an increase of the lipophilicity of these compounds, that, in turn, could be beneficial to their biological activity);[1b,2,10] (ii) we recently reported a versatile synthesis of a series of ferrocene-containing β-aminoketones (Mannich bases, 2-ferrocenoylethyl aryl amines) by aza-Michael addition of aryl amines to the conjugated ketone acryloylferrocene, catalyzed by montmorillonite K-10 and assisted by microwave or ultrasound irradiation.[11] Considering the known carbonyl group reactivity, we realized that these ketones could serve as precursors of the

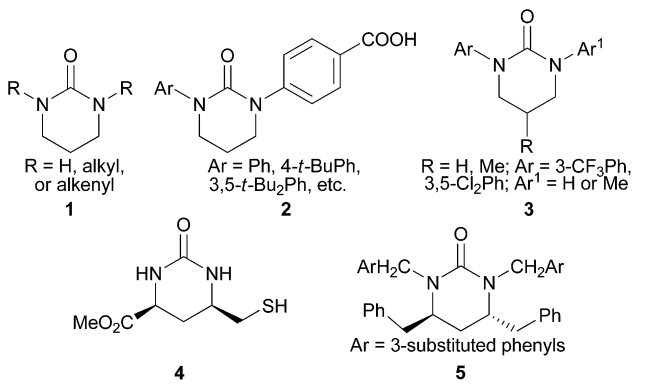

Fig. 1 Some bioactive six-membered cyclic ureas.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectral characterisation (including copies of ^{1}H and ^{13}C NMR spectra) of all new compounds, crystallographic data and CIF files. CCDC 1043324 and 1043325. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra01383f

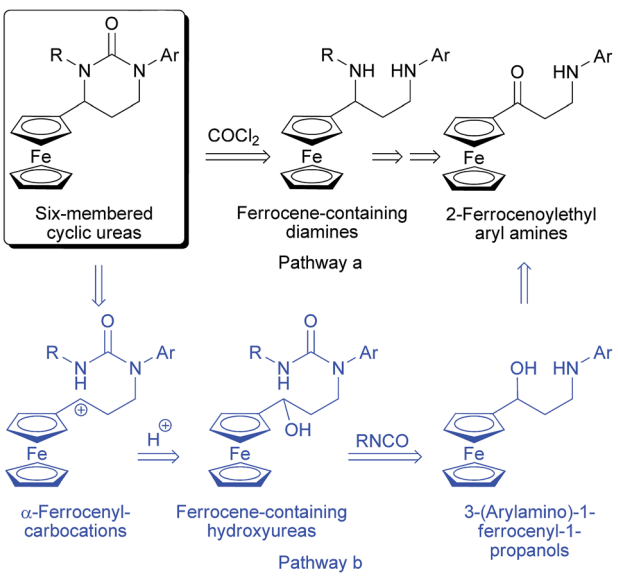
corresponding ferrocene-containing 1,3-diamines which (according to the aforementioned literature reports[8,9]) would represent a starting material in the synthesis of the corresponding six-membered cyclic ureas.

In this communication we report on the synthesis of seventeen new ferrocene-containing six-membered cyclic ureas (1-aryl-4-ferrocenyl-3-phenyltetrahydropyrimidin-2(1*H*)-ones), which were completely characterized by spectral data.

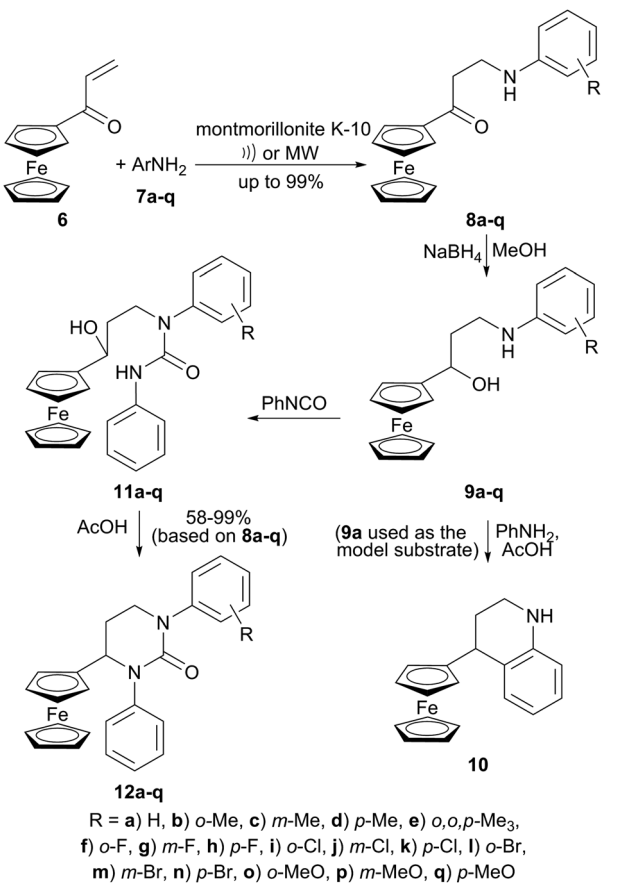
Having a series of 2-ferrocenoylethyl aryl amines at hand, we performed a simple retrosynthetic analysis and envisaged a synthesis of the target six-membered cyclic ureas with the corresponding diamines as key intermediates, as depicted in Scheme 1 (Pathway a). Among several possible approaches to these diamines from 2-ferrocenoylethyl aryl amines – the reduction of the latter and subsequent nucleophilic substitution of the hydroxyl group from the obtained alcohol with an amine seemed to be the most suitable one. The ease of formation of α-ferrocenyl carbocations from 1-ferrocenylalkanols and their well-known stability lied at the heart of this idea. For example, a successful α-ferrocenylalkylation of anilines with 1-ferrocenylethanol, under mild conditions, was reported recently.[12] However, recently, following this procedure, we failed to obtain the product of substitution of the hydroxyl group from 1-ferrocenyl-3-thiapentan-1-ol using diethylamine as the nucleophile;[13] an attempt with aniline as the nucleophile was also unsuccessful. (The successful substitution was accomplished by applying an older method that included acetylation of the starting alcohol before the substitution step[13,14]).

A recently reported successful substitution of the hydroxyl group in 1-ferrocenyl-1-alkanols, promoted by acetic acid,[15] deemed very suitable for the synthesis of the necessary diamines. Thus, the realization of the synthetic plan by Pathway a (Scheme 1) began with the synthesis of the Mannich base 2-ferocenoylethyl phenyl amine (**8a**) (by aza-Michael addition of aniline (**7a**) to acryloylferrocene (**6**), following the known procedure,[11] Scheme 2). After the reduction of this ketone (with sodium borohydride in methanol), the obtained 3-(aminophenyl)-1-ferocenyl-1-propanol (**9a**) was treated with aniline in the presence of acetic acid.[15] However, instead of the desired diamine, we obtained 4-ferrocenyl-1,2,3,4-tetrahydroquinoline (**10**). Apparently, upon protonation, the alcohol loses a water molecule giving a (stable) α-ferrocenyl carbocation electrophilic enough to undergo an intramolecular alkylation of the benzene ring activated by the amine nitrogen.‡

Based on this experience (and, also, being unwilling to use phosgene as the most efficient reagent for the subsequent step of the synthesis), we envisaged an alternative approach to the target ferrocene-containing six-membered cyclic ureas, abandoning the idea of 1,3-diamines as the key intermediates. In fact, we opted for the "reverse order of events" – β-aminoketones → 1,3-aminoalcohols → cyclic ureas; instead of substituting the hydroxyl group before the introduction of the urea functionality, we chose to submit the aminoalcohols to the reaction with an isocyanate. Namely, it is well known that the addition of amines to isocyanates represents the most widely used method for the synthesis of acyclic ureas,[8,16] and this gives the opportunity to design the corresponding β-hydroxy ureas as key intermediates in the target synthesis (Pathway b, Scheme 1). In this way, the role of an α-ferrocenyl carbocation was left for the final step, in which the hydroxyl group was to be substituted (*via* this cation) by an NH group from the formed urea moiety,



Scheme 1 Retrosynthetic analysis.



Scheme 2 Synthesis of tetrahydropyrimidin-2-ones **12a–q**.

assembling the six-membered ring. The idea was tested on the Mannich base **8a**, *i.e.*, *via* the aminoalcohol **9a**, which reacted smoothly (without any particular purification) with phenyl isocyanate affected by a short ultrasonic irradiation. Acetic acid was added to the product (still in the same vessel, *i.e.*, again without isolation or purification) and the mixture irradiated additionally to give, after the usual workup and column chromatography (SiO_2/*n*-hexane–EtOAc, 8 : 2, v/v), the target six-membered cyclic urea **12a** in a good yield (78%).

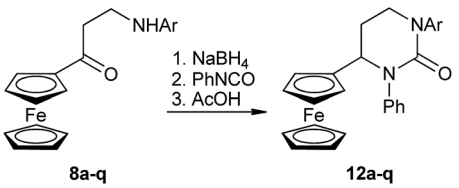
The same procedure was applied for the synthesis of a small library of cyclic ureas (see Scheme 2), and the obtained results are summarized in Table 1. As these results show, this protocol allowed an easy and high yielding (up to 99%) access to ferrocene-containing tetrahydropyrimidin-2-ones **12a–q** starting from the corresponding Mannich bases. These compounds were found to be stable at room temperature for a prolonged time period and could safely be handled in air, but like other ferrocene derivatives, should be stored in closed containers.

Although the reaction of alcohols **9a–q** with phenyl isocyanate and the subsequent intramolecular cyclization of the thus obtained products to cyclic ureas **12a–q** proceeded in "a one pot" manner, the existence of intermediates **11a–q** was inferred from a careful analysis of ^{1}H and ^{13}C NMR spectra of an aliquot of the reaction mixture obtained with **9k**, sampled before the addition of acetic acid (see ESI†).

A plausible mechanism of these transformations is depicted in Scheme 3. In the first reaction step, the NH group of alcohols **9a–q** adds to the C=N double bond of the isocyanate group giving, *via* zwitterions **I**, hydroxyureas **11a–q**. A key step of the overall reaction is an intramolecular cyclization of these intermediates. As depicted in Scheme 3, the reaction starts with the protonation of **11a–q** by acetic acid and dehydration of the resulting oxonium ions **II**, giving α-ferrocenyl carbocations **III**, known to be very stable due to the participation of the ferrocenyl group in the delocalization of the positive charge.[17] A nucleophilic attack of the carbamide nitrogen on the positive centre of these cations affords cations **IV**, which are deprotonated to give the target compounds **12a–q**.

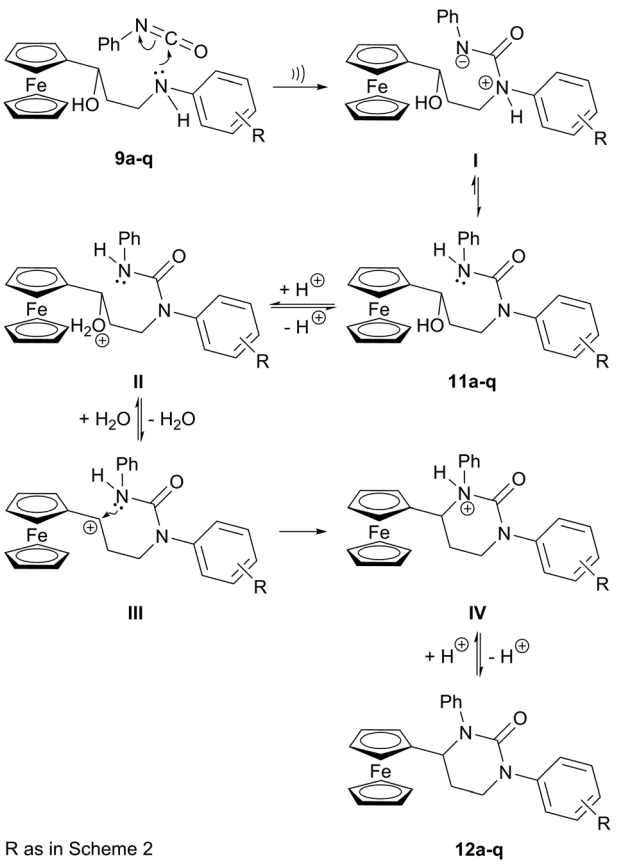
The structures of the synthesized cyclic ureas were corroborated by careful ^{1}H, ^{13}C and 2D NMR spectral analyses. Since the structures of these compounds include only one chiral centre (C4, originating from the corresponding racemic alcohols **9a–q**) they were expected to form the corresponding racemates. However, the spectra of some *ortho*-substituted derivatives revealed the existence of mixtures of two diastereoisomers. Namely, compared to that of **12a**, the number of signals in the ^{13}C NMR spectrum of compound **12b** was found to be almost doubled (some, most probably, must have overlapped). Characteristic signals appearing in the ^{1}H NMR spectra of this compound, like those attributed to the protons of the methyl group (singlet), the C4 methylene group (pseudotriplet $J \sim 4$ Hz) and the unsubstituted cyclopentadiene ring (singlet) appeared as pairs of more or less well-separated analogous pairs of signals (ESI, Fig. S1†). According to the integral ratios of these

Table 1 Synthesis of tetrahydropyrimidin-2-ones **12a–q**



Entry	Product	Ar	Yield[a] (%)
1	**12a**	C_6H_5	78
2	**12b**	2-$CH_3C_6H_4$	83
3	**12c**	3-$CH_3C_6H_4$	86
4	**12d**	4-$CH_3C_6H_4$	80
5	**12e**	2,3,4-$(CH_3)_3C_6H_2$	78
6	**12f**	2-FC_6H_4	84
7	**12g**	3-FC_6H_4	91
8	**12h**	4-FC_6H_4	80
9	**12i**	2-ClC_6H_4	80
10	**12j**	3-ClC_6H_4	88
11	**12k**	4-ClC_6H_4	83
12	**12l**	2-BrC_6H_4	62
13	**12m**	3-BrC_6H_4	68
14	**12n**	4-BrC_6H_4	89
15	**12o**	2-$CH_3OC_6H_4$	99
16	**12p**	3-$CH_3OC_6H_4$	58
17	**12q**	4-$CH_3OC_6H_4$	64

[a] Yields of isolated compounds, based on aminoketones **8a–q**.



Scheme 3 A plausible reaction mechanism of the transformation of alcohols **9a–q** into six-membered cyclic ureas **12a–q**.

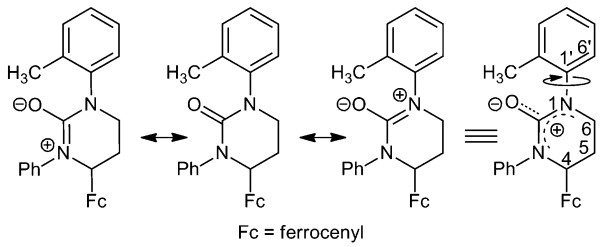


Fig. 2 Resonance structures of **12b**.

protons, we estimated that the obtained product represented a 55 : 45 mixture of two diastereoisomers, even though **12b** contains only a single chiral centre.

An explanation for this phenomenon was much simpler than it looked at the first glance. Namely, participating in the resonance delocalisation, the nitrogen atoms of the urea unit take a trigonal character, as depicted in Fig. 2, causing all atoms of the tetrahydropyirimidin-2-one unit to lie in the same plane, except C5. This induces a high rigidity of the six-membered ring and restricts rotation around the single N1–C1′ bond when C2′ bears a bulky group (for example, a methyl group). This imparts an additional element of (axial) chirality to the molecule, and provides an explanation for the observed diastereoisomerism, *i.e.*, for the appearance of two pairs of enantiomers.

Although we did not obtain crystals of urea **12b** suitable for single crystal X-ray analysis to confirm this claim, monocrystals of **12c** and **12e** were of sufficient quality, and their molecular structures are presented in Fig. 3.[18] Thus, this analysis showed that in **12e** (containing methyl groups in both *ortho* positions) the fragment C6–N1–C2–N3–C4 lies almost in the same plane (torsion angles N1–C2–N3–C4 and N3–C2–N1–C6 were less than 2°). To approximately adopt a coplanar arrangement of this fragment and the benzene ring (this represents the highest energetic barrier to the rotation around N1–C1′ bond), the hydrogen atoms from the methyl groups have to approach the oxygen atom or the protons of C6 methylene group to a distance of less than 1 Å (ESI, Fig. S2†). This molecular event would certainly govern the rotation around the single N1–C1′ bond in this compound, and the same should happen in the case of **12b**.

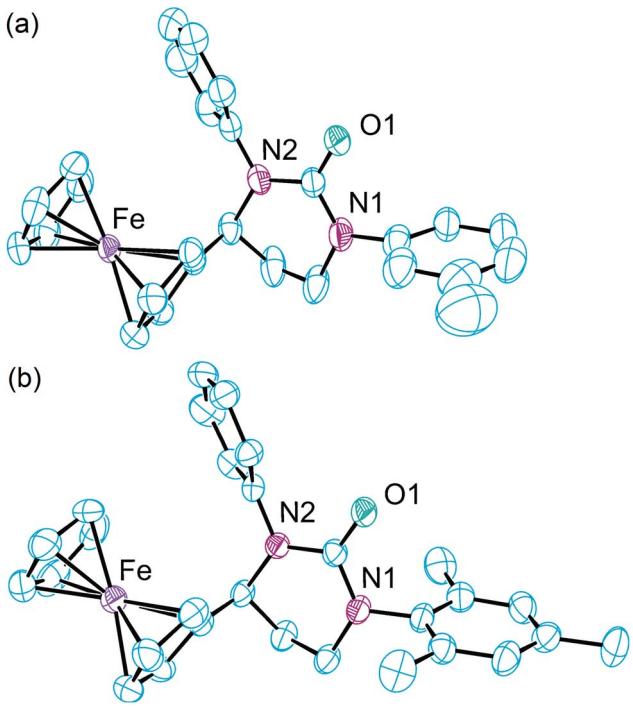


Fig. 3 The molecular structures of (a) **12c** and (b) **12e** (hydrogen atoms are omitted). Displacement ellipsoids are drawn at 30% probability level.[18]

As mentioned, an analogous phenomenon was observed for all other *ortho*-substituted cyclic ureas (**12f**, **12i**, **12l** and **12o**). However, it seems that the rotational energetic barrier for the N1–C1′ bond in these molecules is lower than that in the case of **12b**, so the corresponding signals in the ^{1}H NMR spectra either overlapped or were conformationally broadened or averaged. This interesting occurrence of diastereoisomerism caused by conformational chirality (atropisomerism) indeed needs (and deserves) additional study. Namely, enantiomeric forms of alcohols **9a–q**, obtained by an asymmetric reduction of Mannich bases **8a–q**, would certainly give enantiomeric forms of cyclic ureas **12a–q**, due to the known feature of α-ferrocenyl carbocations – to retain the configuration during nucleophilic substitutions.[19] If that were the case, cyclic ureas like **12c** would appear as the mixture of two diastereoisomers, and not as the mixture of two pairs of enantiomers. The use of aminoalcohols carrying a more sterically demanding group in the *ortho* position might also be useful for such investigations.

Conclusions

In conclusion, herein, we presented a versatile protocol for the synthesis of ferrocene-containing six-membered cyclic ureas – 1-aryl-4-ferrocenyl-3-phenyltetrahydropyrimidin-2(1*H*)-ones – starting from the corresponding β-(arylamino)ketones, compounds readily available through the aza-Michael addition of the corresponding anilines to acryloylferrocene. The formation and reactivity of an α-ferrocenyl carbocation represents the key step in this synthesis.

Acknowledgements

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Notes and references

‡ Although irrelevant for the current work, this reaction is certainly very interesting and deserves separate investigations, which have been already initiated (the results will be reported in the near future).

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18 Crystal data for **12c**: $C_{27}H_{26}FeN_2O$, M = 356.81, orthorhombic, a = 23.4076(10) Å, b = 10.6422(3) Å, c = 8.9673(3) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, V = 2233.83(14) Å^3, T = 293(2) K, space group $Pca2_1$, Z = 4, μ(MoKα) = 0.696 mm^{-1}, 18343 reflections measured, 5273 independent reflections (R_{int} = 0.0216). The final R_1 values were 0.0402 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.0989 ($I > 2\sigma(I)$). The goodness of fit on F^2 was 1.044. CCDC number CCDC 1043324. Crystal data for **12e**: $C_{29}H_{30}FeN_2O$, M = 356.81, triclinic, a = 8.9564(4) Å, b = 11.9843(5) Å, c = 22.8058(10) Å, α = 79.735(4)°, β = 88.568(4)°, γ = 89.935(4)°, V = 2407.94(18) Å3, T = 293(2) K, space group $P\bar{1}$, Z = 4, μ(MoKα) = 0.650 mm^{-1}, 30636 reflections measured, 8712 independent reflections (R_{int} = 0.0441). The final R_1 values were 0.1094 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.3031 ($I > 2\sigma(I)$). The goodness of fit on F^2 was 1.078. CCDC number CCDC 1043325.†

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