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Influence of substitution on kinetics and mechanism of ring transformation of substituted *S*-[1-phenylpyrrolidin-2-on-3-yl]-isothiuronium salts† ‡

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Twelve new substituted *S*-(1-phenylpyrrolidin-2-on-3-yl)isothiuronium bromides and twelve corresponding 2-imino-5-(2-phenylaminoethyl)thiazolidin-4-ones have been prepared and characterised. Kinetics and mechanism of transformation reaction of *S*-[1-(4-methoxyphenyl)pyrrolidin-2-on-3-yl]isothiuronium bromide **1a** and its *N*,*N*-dimethyl derivative **5a** into corresponding substituted thiazolidin-4-ones **2a** and **6a** have been studied in aqueous solutions of amine buffers (pH 8.1–11.5) and sodium hydroxide solutions (0.005–0.5 mol l^{-1}) at 25 °C and at $I = 1$ mol l^{-1} under pseudo-first-order reaction conditions. The kinetics observed show that the transformation reaction is subject to general acid–base, and hydroxide ion catalyses. Acid catalysis does not operate in the transformation of **1a**; the rate-limiting step of the base-catalysed transformation is the decomposition of bicyclic tetrahedral intermediate $\mathbf{In}^{\pm}$ and the Brønsted dependence is non-linear ($pK_a \approx 9.8$). In the case of derivative **5a** both base and acid catalyses make themselves felt. In the base catalysis, the rate-limiting step consists of the decomposition of bicyclic intermediate **In**, and the Brønsted dependence is linear ($\beta = 0.9$; $pK_a > 11.5$). The acid-catalysed transformation of **5a** also proceeds *via* the intermediate **In**, and the reaction is controlled by diffusion ($\alpha \approx 0$). With compound **5a** in triethylamine and butylamine buffers, the general base catalysis changes into specific base catalysis. The effect of substitution in aromatic moiety of compounds **1a**–**h** and **3a**–**h** on the course of the transformation reaction has been studied in solutions of sodium hydroxide (0.005–0.5 mol l^{-1}) at 25 °C by the stopped-flow method. The electron-acceptor substituents 4-NO_2 and 4-CN do not obey the *Hammett* correlation, which is due to a suppression of cross-conjugation in the ring-closure step of the transformation reaction.

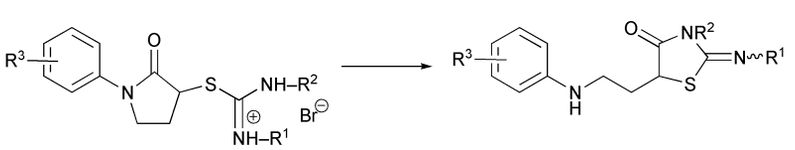
Introduction

In our earlier paper[1] we studied the kinetics and mechanism of transformation reaction of *S*-[1-(4-methoxyphenyl)pyrrolidin-2-on-3-yl]-*N*-methylisothiuronium bromide (**3a**) to 2-methylimino-5-[2-(4-methoxyphenylamino)ethyl]thiazolidin-4-one (**4a**). It was found that the transformation reaction goes by several reaction pathways, being catalysed by both the acidic and the basic components of the buffer (general acid and base catalysis). The rate-limiting step consists of the splitting off of the proton from the tetrahedral intermediate ($pK_a = 10$) or (in tertiary amine buffers) decomposition of the negatively charged intermediate. The aim of the present work is to study the effect of substitution both in the aromatic skeleton and at one or both nitrogen atoms of the isothiuronium moiety on the detailed mechanism of this transformation reaction (Scheme 1).

Results and discussion

The kinetics of transformation reaction of isothiuronium salts **1a** and **5a** into **2a** and **6a**, respectively, were studied under the conditions of pseudo-first-order reaction in aqueous buffers containing tris(hydroxymethyl)aminomethane, morpholine, 2-methoxyethylamine, ethanolamine, *N*-methylpyrrolidine, triethylamine and butylamine, and in solutions of sodium hydroxide at 25 °C at the ionic strength $I = 1$ mol l^{-1} (the substrate concentration $c_S = 5 \times 10^{-5}$ mol l^{-1}). The spectral records showed well-developed isosbestic points. The overall rate of the transformation reaction followed under pseudo-first-order conditions can be expressed by Eqn. (1).

$$v = k_{obs} c_s \quad (1)$$



1a-h $R^1 = R^2 = H$
3a-h $R^1 = H$, $R^2 = CH_3$
5a $R^1 = R^2 = CH_3$

2a-h $R^1 = R^2 = H$
4a-h $R^1 = H$, $R^2 = CH_3$
6a $R^1 = R^2 = CH_3$

R^3 = a: 4-OCH_3; **b:** H; **c:** 4-Cl; **d:** 3-Cl; **e:** 3-CF_3; **f:** 3-NO_2; **g:** 4-CN; **h:** 4-NO_2

Scheme 1

† Dedicated to Professor Vladimr Macháček on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: observed rate constants and corrected rate constants in all buffers for **1a** ⟶ **2a** and **5a** ⟶ **6a**, and in sodium hydroxide solutions for **1a**–**h** ⟶ **2a**–**h** and **3a**–**h** ⟶ **4a**–**h**, and spectral record of the reaction of **5a** to **6a** in aqueous morpholine buffer (1 : 1) at $c_{Buffer} = 0.150$ mol l^{-1}. See http://www.rsc.org/suppdata/ob/b4/b401866d/

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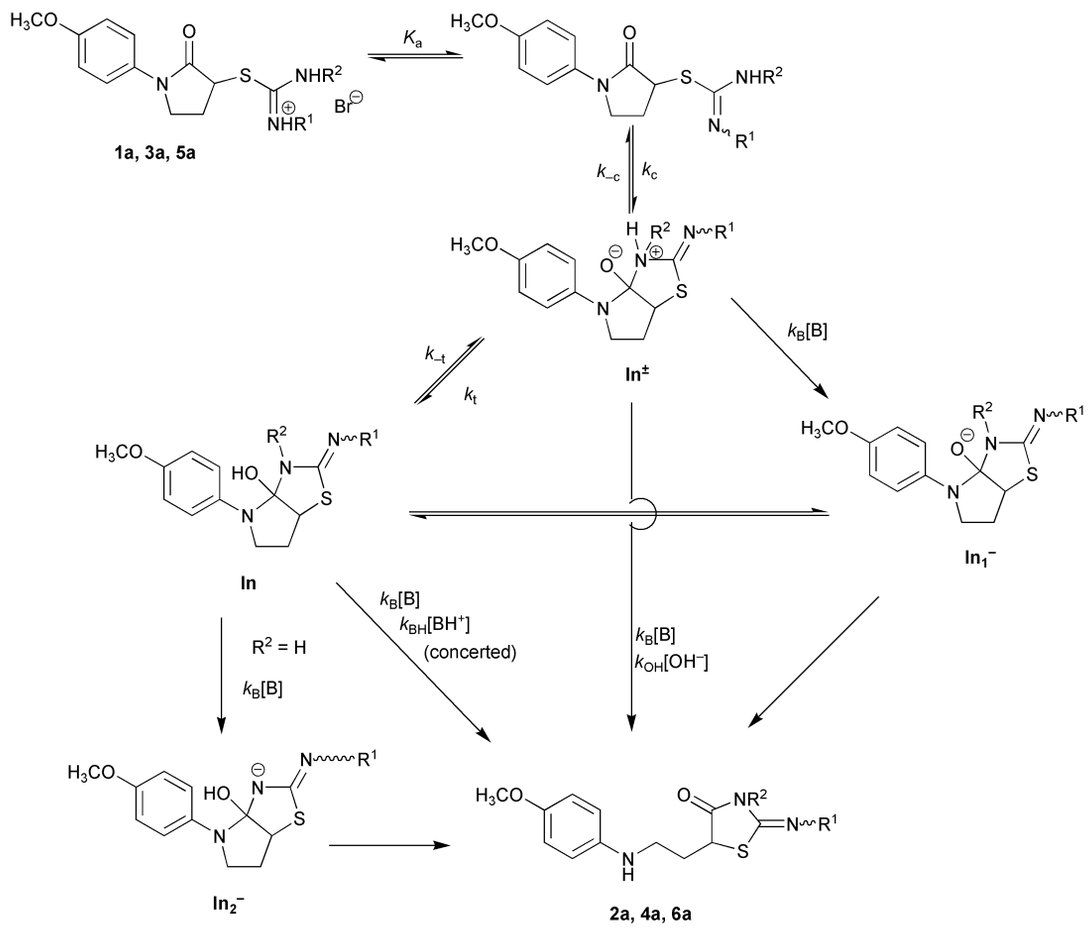


Scheme 2

Since the reactive species of the transformation reaction is the free amino group of thiourea (the protonated isothiuronium salt does not practically undergo the ring closure), it was necessary to define[1] the corrected rate constant k_{cor}, referenced to the concentration of the non-protonated reactive form of isothiourea, by means of Eqn. (2).

$$k_{cor} = k_{obs}\,(1 + 10^{(pK_a - pH)}) \qquad (2)$$

The calculation of individual corrected rate constants from the observed constants k_{obs} by Eqn. (2) required determination of the pK_a values of isothiuronium salts **1a** and **5a**. The pK_a values found by us strongly depended on substitution at the nitrogen atoms in the isothiuronium moiety of the molecule: pK_a (**1a**) = 7.30 ± 0.05, pK_a (**3a**)[1] = 8.75 ± 0.10, and pK_a (**5a**) = 10.30 ± 0.08. These measured values vary within 0.5 units, the influence on acidity in their comparison being unexplainable by mere $+I$ effect of the methyl group(s). A partial interpretation can be seen in the formation of an intramolecular hydrogen bond giving a seven-membered cycle (Fig. 1). From Fig. 1 it can be seen that splitting off of the exocyclic proton will be much more favourable than that of the endocyclic proton.

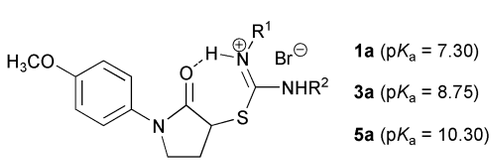


Fig. 1

A similarly distinct but opposite difference in pK_a values due to methyl substitution was also observed[3] in the case of substituted *N*-acetylthioureas.

Effect of methyl substitution on kinetics and mechanism of transformation reaction in amine buffers

The dependence of the observed rate constants k_{obs} on the concentrations of individual buffer components shows that the transformation reaction of isothiuronium salts **1a** and **5a** into **2a** and **6a**, respectively, has the same course as in the previous case (**3a** ⟶ **4a**).[1] This means that the reaction is general-base- and/or general-acid-catalysed, which can be expressed by Eqn. (3).

$$k_{cor} = k_{OH}\,[OH^-] + k_B\,[B] + k_{BH}\,[BH] \qquad (3)$$

The dependence of log $k_{extrapol}$ ($k_{extrapol}$ are k_{obs} values extrapolated to zero buffer concentration) on the pH values of the individual buffers are linear with slope 1 in both cases of the transformation reaction (**1a** and **5a**), as in the transformation[1] **3a** ⟶ **4a**. Likewise, the dependence of k_{OH} *vs.* [OH^-] is linear and crosses the origin of coordinates, which indicates the absence of a non-catalysed reaction (k_0 = 0). The following general scheme (Scheme 2) is plausible for the transformation reaction of all the isothiuronium salts (**1a**,**3a**,**5a**) into thiazolidin-4-ones (**2a**,**4a**,**6a**).

The general scheme (Scheme 2) indicates that the transformation reaction of isothiuronium salts **1a**, **3a** and **5a** can, in principle, go by several reaction pathways *via* several different intermediates. The most probable main reaction pathways and/or the respective rate-limiting steps for the individual derivatives can be determined from the Brønsted dependences. From these it is possible to estimate the type of acid–base catalysis and, in favourable cases, to determine the pK_a values of the intermediates too.

Transformation reaction 1a ⟶ 2a

The dependence of corrected rate constants, k_{cor}, on the concentration of the basic component in primary amine

Table 1 Values of catalytic constants k_B, k_{BH} determined in individual buffers for **1a** and **5a**, and pK_a values of the protonated amine bases

Buffer	pK_a	k_B (l mol^{-1} s^{-1}) **1a**	k_{BH} (l mol^{-1} s^{-1}) **5a**	k_{BH} (l mol^{-1} s^{-1}) **5a**
Butylamine	11.38	1.726	11.60[a]	—
Ethanolamine	9.68	0.670	0.340	0.540
Methoxyethylamine	9.45	0.587	0.200	0.770
Morpholine	8.82	0.160	0.050	0.590
TRIS	8.10	0.019	0.012	0.404

[a] Calculated from the non-linear dependence using Eqn. (4).

buffers (Fig. 2) indicates that the transformation reaction of isothiuronium salt **1a** is catalysed only by the basic buffer component and hydroxide ion (*i.e.* $k_{BH} = 0$), in contrast to the behaviour of **3a** published earlier.[1]

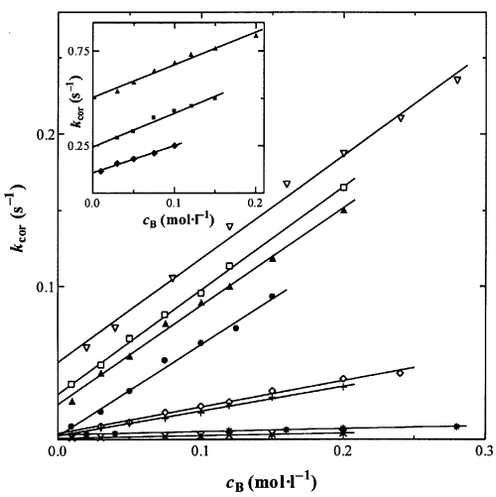


Fig. 2 Dependence of corrected rate constant (k_{cor}) of transformation **1a** ⟶ **2a** on concentration of basic buffer component (c_B) in tris(hydroxymethyl)aminomethane buffers [(1 : 1), pH = 8.43 (×); (4 : 1b), pH = 8.97 (*)], morpholine buffers [(1 : 1), pH = 8.88, (+); (3 : 1b), pH = 9.37 (◊)], 2-methoxyethylamine buffers [(1 : 3a), pH = 9.31 (●); (2 : 1b), pH = 10.02 (▲)]; ethanolamine buffers [(2 : 1b), pH = 10.08 (□); (4 : 1b), pH = 10.36, (▽)] and butylamine buffers (inset): [(1 : 3a), pH = 10.34 (◆); (1 : 1), pH = 10.98 (■); (2 : 1b), pH = 11.21 (▲)]. Note: a - acidic; b - basic.

Table 1 presents the catalytic constants k_B for compounds **1a** and **5a** determined in the individual buffers and calculated from experimental dependences (Fig. 2) of k_{cor} on the basic buffer component (c_B). The k_B constants thus obtained were plotted against the pK_a values of the protonated bases of the individual buffers to give the Brønsted dependence (Fig. 3). With

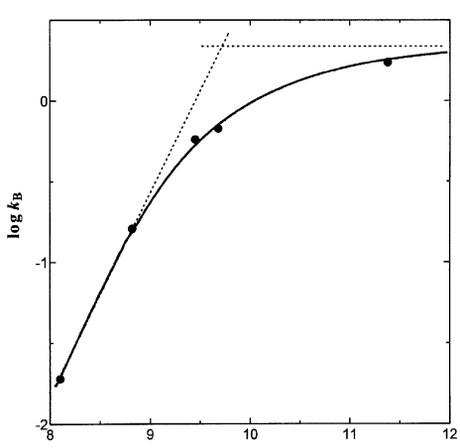
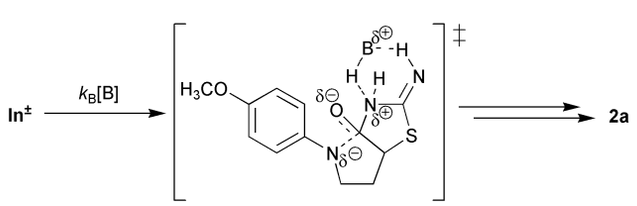


Fig. 3 Brønsted dependence of log k_B of transformation **1a** ⟶ **2a** on pK_a of acid component of amine buffer catalyst.

increasing basicity of buffer, the value of the Brønsted coefficient β decreases from about 1 to values near to 0.

This course of dependence is of a similar nature to that found earlier[1] for reaction **3a** ⟶ **4a**. However, in the present case, the shoulder in the dependence occurs somewhat sooner, *viz.* in the region p$K_a \approx 9.8$. The rate-limiting step of transformation **1a** ⟶ **2a** must involve either decomposition of **In** as in transformation **3a** ⟶ **4a** or concerted base-catalysed decomposition of **In**$^{\pm}$.

The pathway *via* intermediate **In** can only be significant in buffers of low pK_a, where there is a fast proton transfer from nitrogen to oxygen of intermediate (**In**$^{\pm}$ ⟶ **In**) followed by its base-catalysed decomposition. In buffers with a higher pK_a, where the base-catalysed formation of product is diffusion-controlled (the plateau region in the Brønsted dependence, where $k_B/[\mathbf{In}^{\pm}] > 10^8$ s^{-1}), direct decomposition of **In**$^{\pm}$ is more likely. The fact that the break in the Brønsted dependence occurs at a relatively high value p$K_a \approx 9.8$ can be explained by operation of a pre-association mechanism.[4] Analogous intermediates should have pK_a values about one unit lower (*cf.* hydrazinolysis of benzylpenicillin[5]). The pre-association mechanism makes itself felt in cases where the acidity of the intermediate undergoing decomposition and that of the protonated general base catalysing its decomposition are expressed by similar pK_a values. The pK_a value of the intermediate decomposing in the rate-limiting step is *ca.* 0.3 units lower than the pK_a value of the intermediate operating in the transformation **3a** ⟶ **4a**. This small difference in the pK_a values of the two intermediates indicates that the intermediates are different in the two cases, because it can be presumed that the difference in the pK_a values should be similar to that of the starting isothiuronium salts (Δp$K_a = 1.5$). The operation of a pre-association mechanism is also indicated by the possibility of formation of an intramolecular hydrogen bond, where a six-membered cycle is formed in the transition state (Scheme 3).



Scheme 3

Transformation reaction 5a ⟶ 6a

In the case of transformation reaction of isothiuronium salt **5a** it was found that the corrected rate constants determined in tris(hydroxymethyl)aminomethane, morpholine, 2-methoxyethylamine, and ethanolamine buffers give parallel straight lines indicating dependence on neither the acid buffer component nor the base buffer component. Therefore, it follows that both general acid and general base catalyses make themselves felt. Fig. 4 presents the dependence of corrected rate constants on buffer concentration, wherefrom the individual catalytic constants (k_B and k_{BH}) were evaluated by the method given in a previous paper[1] (Table 1).

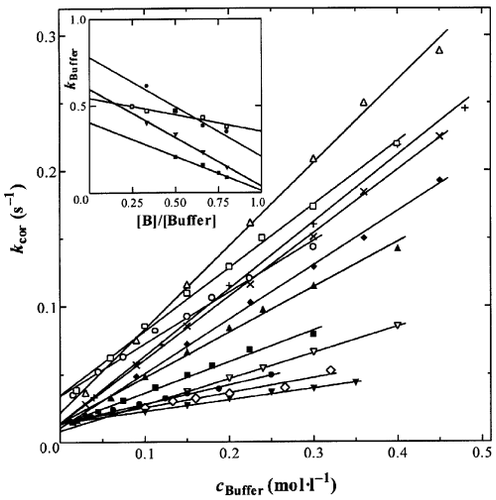
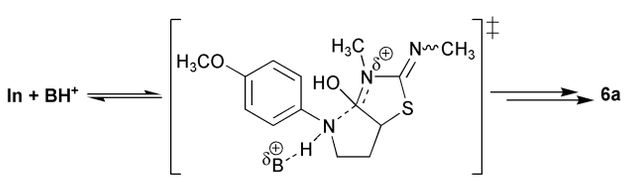


Fig. 4 Dependence of corrected rate constant, k_{cor} (s^{-1}), on buffer concentration, c_{buffer} (mol l^{-1}), measured at 25 °C in tris(hydroxymethyl)aminomethane buffers [▽ (1 : 1) pH = 8.42; ◊ (1 : 3b) pH = 8.82; ▼ (1 : 4b) pH = 8.97], morpholine buffers [◆ (2 : 1k) pH = 8.66; ▲ (1 : 1) pH = 8.92; ■ (1 : 2b) pH = 9.26; ● (1 : 4b) pH = 9.65], ethanolamine buffers [+ (3 : 1k) pH = 9.25; × (2 : 1k) pH = 9.54] and 2-methoxyethylamine buffers [Δ (2 : 1k) pH = 9.34; □ (1 : 1) pH = 9.68; ○ (1 : 2b) pH = 10.00]. Inset: (■) tris(hydroxymethyl)aminomethane, (▼) morpholine, (●) 2-methoxyethylamine and (□) ethanolamine. Note: a - acidic; b - basic.

From Table 1 and/or from Fig. 4 (inset) it is obvious that the acid-catalysed pathway, which does not operate at all in the case of non-substituted derivative **1a**, and which is a minor reaction pathway[1] for compound **3a** (k_{BH} is about two orders of magnitude lower than k_B), becomes the dominant reaction pathway for **5a**. The k_{BH} values oscillate about the value of 0.6, and the value of the Brønsted coefficient α approaches zero (Table 1). If the α values are near to zero, proton transfer is thermodynamically favourable, and the reaction approaches a diffusion-controlled mechanism. Such a proton transfer takes place in cases where the intermediate is a very strong base. The most basic intermediate that can decompose to product under acid catalysis is—in our case—the intermediate **In** only (Scheme 4).



Scheme 4

The base-catalysed transformation **5a** ⟶ **6a** cannot occur by direct decomposition of $\mathbf{In}^{\pm}$ as in the case of transformation of **1a** or **3a**, because in this case the Brønsted dependence is linear in the whole range (Fig. 5), and the value of the coefficient is $\beta = 0.9$. The second reaction pathway through intermediate $\mathbf{In_2}^-$ cannot be considered either, because the endocyclic nitrogen atom carries a methyl group. Thus, the only remaining possibility is the reaction pathway through intermediate **In**. The decomposition of **In** can proceed either by a single-step mechanism or by two steps *via* intermediate $\mathbf{In_1}^-$. From the Brønsted dependence it is clear that the pK_a value of intermediate **In** must be higher than 11.5, which corresponds to splitting off of the proton from the oxygen atom. This presumption stands in accordance with the literature[6,7] giving the value pK_a = 12.7 for analogous tetrahedral intermediates.

The course of transformation reaction in triethylamine and butylamine buffers is entirely different from the previous cases (Fig. 6).

Table 2 Values of catalytic constants k_B, and ratios k^R_{BH}/k_p determined in individual buffers for **5a**, and pK_a values of the protonated amine bases

Buffer	pK_a	k_B (l mol^{-1} s^{-1})	k^R_{BH}/k_p
Butylamine	11.38	11.6 ± 0.5	45±3
Triethylamine	11.08	8.4 ± 0.7	67±8

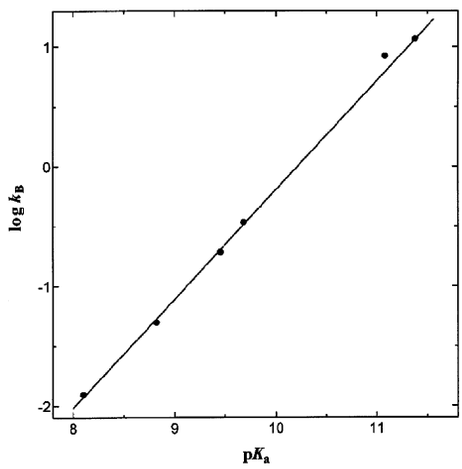


Fig. 5 Brønsted dependence of log k_B (●) on pK_a of protonated amine bases for reaction **5a** ⟶ **6a**.

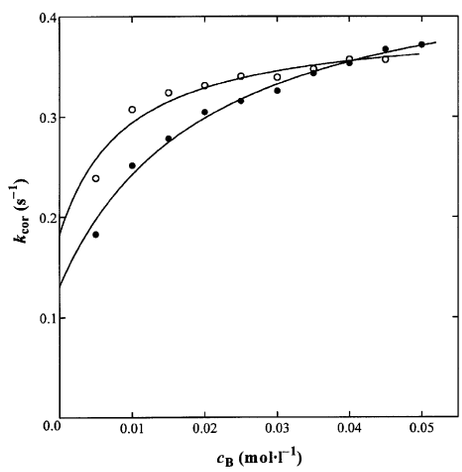


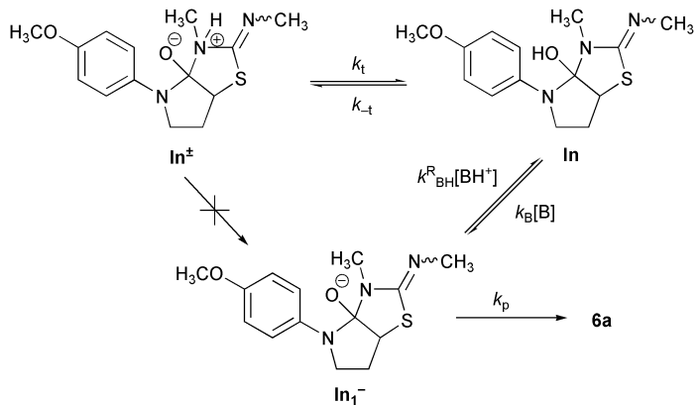
Fig. 6 Dependence of k_{cor} on concentration of basic buffer component (c_B; mol l^{-1}) measured at 25 °C in butylamine buffer (1 : 1) pH = 11.25 (●) and triethylamine buffer (1 : 1), pH = 11.11 (○).

The non-linear increase in the observed rate constant with increasing buffer concentration can be interpreted by a change in the rate-limiting step, as in the case[1] of transformation **3a** ⟶ **4a**, where the general base catalysis changes to specific base catalysis. The points in Fig. 6 are experimental values, and the curve represents the theoretical course according to[1] Eqn. (4).

$$k_{cor} = k_{OH}[OH^-] + \frac{k_B[B]}{1 + \frac{k^R_{BH}}{k_p}[BH]} \qquad (4)$$

The change in rate-limiting step can be expressed by Scheme 5.

Table 2 presents the values of the k_B constants calculated from Eqn. (4). These k_B values represent the base-catalysed decomposition of intermediate **In** ⟶ $\mathbf{In_1}^-$ (Scheme 5). At low concentrations of buffer, and hence also low concentrations of acid buffer component, this step is rate limiting, and the dependence of k_{cor} on the basic buffer component (Fig. 6) is linear. As the buffer concentration increases, the concentration of acid buffer component increases too, and the reverse proton-



Scheme 5

ation $\mathbf{In_1}^- \longrightarrow \mathbf{In}$ begins to make itself felt kinetically, which is characterised by the constant k^R_{BH}, and the slope of dependence of k_{cor} *vs.* c_B will gradually approach zero. In the limiting case, when this slope is zero (the specific base catalysis), $\mathbf{In_1}^-$ and **In** are in equilibrium, and the transformation $\mathbf{In_1}^- \longrightarrow$ **6a** (k_p) becomes the rate-limiting step. Fitting of the experimentally measured points by means of Eqn. (4) can only give the values of k_B and the ratio k^R_{BH}/k_p, where the constant k_p corresponds to the decomposition to products (Table 2). The determined values k_B lie at the Brønsted dependence (Fig. 5).

Effect of substitution in the ring on kinetics and mechanism of transformation reaction in sodium hydroxide solutions

The transformation reaction of isothiuronium salts **1a**–**h** and **3a**–**h** was also followed in sodium hydroxide solutions of 0.05–0.5 M concentration. Since in these solutions all the isothiuronium salt is converted into the reactive isothiourea, no correction of observed rate constant for pH is necessary ($k_{obs} = k_{cor}$). Figs. 7 and 8 show that the dependence is linear for all the substituents, which means that the reaction is of the first order in OH^- within the whole concentration range. All the dependences cross the origin of coordinates, wherefrom it follows that the non-catalysed reaction is insignificant ($k_0 = 0$), hence $k_{obs} = k_{OH}[OH^-]$. Moreover, using HPLC-MS spectroscopy we confirmed that all the derivatives studied only undergo the given transformation reaction within the whole concentration range of sodium hydroxide, *i.e.* no side and subsequent reactions are present. By plotting log k_{OH} of the individual derivatives against the σ constants we obtained the Hammett correlation depicted in Fig. 9. This graph shows that both dependences are

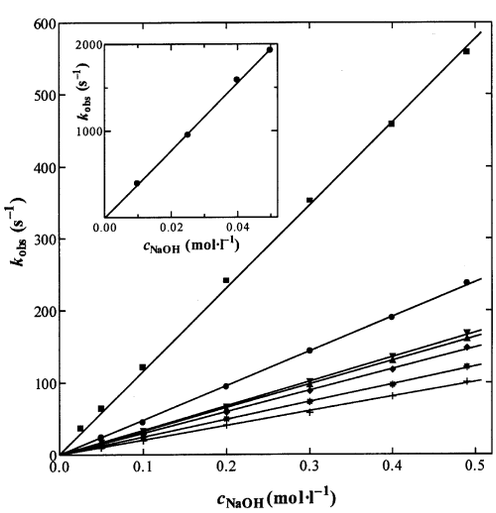


Fig. 7 Dependence of observed rate constants, k_{obs} (s^{-1}) on sodium hydroxide concentration for the substances studied: **1a** (+), **1b** (*), **1c** (◆), **1d** (▲), **1e** (▼), **1f** (●), **1g** (■). Inset: **1h** (●).

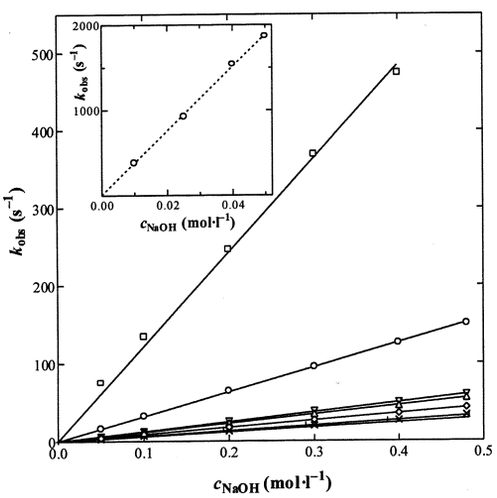


Fig. 8 Dependence of observed rate constants, k_{obs} (s^{-1}) on sodium hydroxide concentration for the substances studied: **3a** (|), **3b** (×), **3c** (◊), **3d** (Δ), **3e** (▽), **3f** (○), **3g** (□). Inset: **3h** (○).

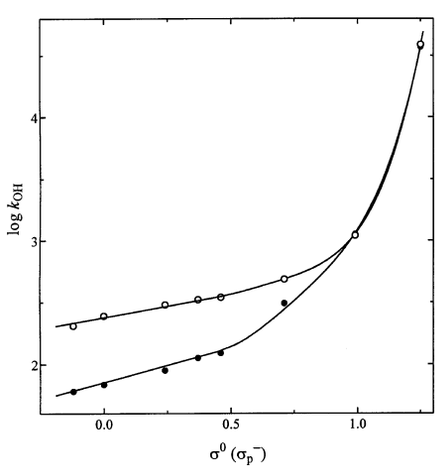
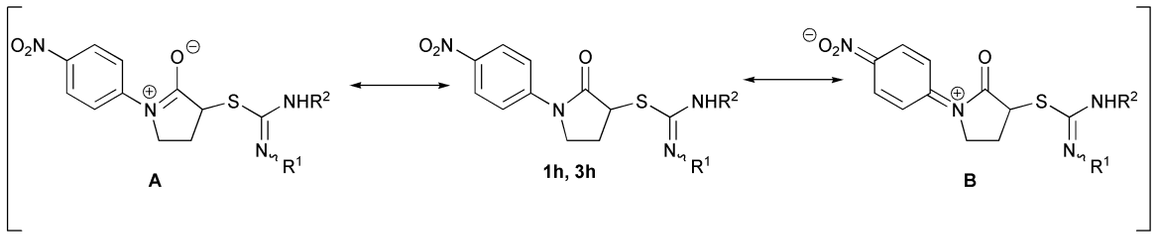


Fig. 9 Hammett dependence of log k_{OH} on σ^0 and/or σ_p^- for the recyclisation reactions of **1a**–**h** (○) and **3a**–**h** (●).

linear with a slope of about 0.4–0.5 for substituents having σ constants below *ca.* 0.5. With higher σ constants, $\sigma > 0.5$ (3-NO_2, 4-CN, and 4-NO_2), the transformation reaction is gradually accelerated, the progressive character of the dependence remaining unchanged even after application of σ_p^- constants (correction for direct conjugation between substituent and reaction centre).

Similar behaviour was observed earlier in the case of base-catalysed hydrolysis of substituted formanilides[8] and their *N*-methyl derivatives,[9] where the rate-limiting step involves splitting off of substituted aniline. An acceleration of hydrolysis by *ca.* 2–4 orders of magnitude was observed with 4-nitro-



Scheme 6

phenylformamide and its *N*-methyl derivative, which was interpreted by a change in symmetry of the transition state of the reaction involving the C–N bond splitting.[8]

The reactions of substrates **1a**–**h** and **3a**–**h** with hydroxide ion are subject to general base catalysis, the decomposition of intermediate $\mathbf{In}^{\pm}$ being the rate-limiting step of the reaction. In the case of specific base catalysis, almost all the intermediate $\mathbf{In}^{\pm}$ would be present in the form of anion $\mathbf{In_I}^{-}$, and the reaction rate would be independent of OH^- concentration. Since the reaction is diffusion-controlled already in basic buffers, the rate-limiting step consists of the encounter between $\mathbf{In}^{\pm}$ and solvated hydroxide ion, and the C–N bond cleavage has no effect on the reaction rate, regardless of whether it proceeds simultaneously with the N–H bond cleavage or after it. The considerable effect of electron-acceptor substituents on the reaction rate can be explained as follows: in the ring-closure step, *i.e.* the attack of carbonyl group by amino group (formation of $\mathbf{In}^{\pm}$), cross conjugation makes itself felt in a negative way (Scheme 6, structure **A**). On the other hand, a strong electron acceptor at the 4-position removes this negative effect, *i.e.* structure **B** is more significant. The relative stability of the intermediate $\mathbf{In}^{\pm}$ formed (and thus also its concentration) will strongly increase in the case of compounds **1h** and **3h**, which will strongly accelerate the reaction with hydroxide ion.

Conclusions

In the case of the transformation reaction studied, the number of methyl substituents at the amino groups of an isothiuronium skeleton was varied. In the transformation reaction, one of the amino groups reacts as an intramolecular nucleophile and the other becomes a substituent of the thiazolidine cycle formed. The ring-closure step of the transformation reaction is kinetically significant before the rate-limiting step; only the next decomposition of bicyclic intermediates is the rate-limiting step. The stereo-electronic effect of methyl substitution was the most distinct when comparing the non-substituted derivative **1a** and *N,N*-dimethyl derivative **5a**. The *N,N*-dimethyl substitution quite unexpectedly affected the pK_a value of the starting isothiuronium salt **5a** as compared with **1a** ($\Delta pK_a = 3$). Less affected were the pK_a values of the individual intermediates. In decomposition of the most basic intermediate **In** of compound **5a** ($pK_a > 11.5$), the acid-catalysed decomposition represents the dominant pathway of the transformation reaction. With the most acidic derivative, **1a**, the acid catalysis practically does not make itself felt (pK_a of the intermediate is *ca.* 9.8). On the other hand, however, the values k_B at lower values pK_a of the buffers were comparable within one order of magnitude for all the derivatives (**1a**,**3a**,**5a**). The second part of this paper deals with the effect of substitution in the aromatic moiety of compounds **1** and **3**: it was found that electron-acceptor groups, such as 4-NO_2 and 4-CN, strongly accelerate the transformation reaction, and these substituents do not fit the Hammett correlation. This deviating behaviour is due to suppression of cross conjugation in the ring-closure step of the transformation reaction, and hence to an increase in actual concentration of the decomposing intermediate $\mathbf{In}^{\pm}$.

Experimental

The kinetic measurements were carried out on an HP UV/VIS 8453 Diode Array apparatus in 1 cm closeable cells at 25 °C. First a suitable wavelength was chosen for the kinetic measurements on the basis of the spectra scanned from 200 to 1000 nm. Then the cell was always charged with 2 ml aqueous amine buffer solution. After attaining the chosen temperature, 10 µl methanolic solution of the substrate **1**, **3** or **5** was added so that the resulting substrate concentration would be about 5×10^{-4} mol l^{-1}. The measurements of reactions with half-lives below 2 s (in aqueous triethylamine buffer solutions and aqueous sodium hydroxide solutions) were carried out using a Diode Array Stopped-Flow SX.18 MV-R (Applied Photophysics) apparatus. The observed pseudo-first-order rate constants k_{obs} were calculated from the measured time dependence of absorbance with the help of an optimisation program.

The dissociation constant of isothiuronium salt **1a**, pK_a = 7.30 ± 0.05, was determined by potentiometric titration of an aqueous solution of the substrate (2 ml; $c = 5 \times 10^{-3}$ mol l^{-1}) using a TITRALAB 3 (Radiometer Copenhagen) apparatus with glass and saturated calomel electrode system at 25 °C. The titration was carried out with 0.1 mol l^{-1} solution of tetrabutylammonium hydroxide in absolute methanol, and it was repeated three times. Benzoic acid was used as the standard (pK_a = 4.20). The dissociation constant of isothiuronium salt **5a**, pK_a = 10.3 ± 0.1, was determined spectrophotometrically from initial spectra in aqueous butylamine buffers.

Syntheses of substituted *S*-(1-phenylpyrrolidin-2-on-3-yl)-isothiuronium bromides **1b**–**g** and **3b**–**g**, and substituted 2-imino-5-[(2-phenylamino)ethyl]thiazolidin-4-ones **2b**–**g** and **4b**–**g**, were carried out according to a procedure described earlier[2] for compounds **1a**, **1h**, **2a**, **2h**, **3a** and **3h**.

S-(1-Phenylpyrrolidin-2-on-3-yl)isothiuronium bromides

1b, yield 78%, mp 194–197 °C. ^{1}H-NMR 2.15 and 2.78 (2H, 2 × m, CH_2), 3.99 (2H, m, NCH_2), 5.07 (1H, t, J = 8.8, SCH), 7.25 (1H, t, J = 7.4, Ar H-4), 7.46 (2H, t, J = 7.6, Ar H-3,5), 7.69 (2H, d, J = 8.0, Ar H-2,6), 9.27 and 9.52 (4H, 2 × br s, 2 × NH_2); ^{13}C-NMR 24.5 (CH_2), 45.9 (S–CH), 46.9 (NCH_2), 120.2 (Ar C-2,6), 125.4 (Ar C-4), 129.0 (Ar C-3,5), 138.6 (Ar C-1), 168.8 (C=N), 170.3 (C=O).

Anal. C, 41.49; H, 4.59; Br, 25.02; N, 13.19; S, 10.01. $C_{11}H_{14}BrN_3OS$ requires C, 41.78; H, 4.46; Br, 25.27; N, 13.29; S, 10.14%.

1c, yield 72%, mp 216–219 °C. ^{1}H-NMR 2.19 and 2.77 (2H, 2 × m, CH_2), 3.98 (2H, m, NCH_2), 5.00 (1H, t, J = 8.9, SCH), 7.54 (2H, AA′XX′, J = 9.0, Ar H-3,5), 7.75 (2H, AA′XX′, J = 8.9, Ar H-2,6), 9.24 and 9.45 (4H, 2 × br s, 2 × NH_2); ^{13}C-NMR 24.4 (CH_2), 45.8 (S–CH), 46.7 (NCH_2), 121.7 (Ar C-2,6), 128.9 (Ar C-3,5), 129.1 (Ar C-4), 137.5 (Ar C-1), 168.5 (C=N), 170.4 (C=O).

Anal. C, 37.76; H, 3.88; N, 11.84; S, 9.09. $C_{11}H_{13}BrClN_3OS$ requires C, 37.68; H, 3.74; N, 11.98; S, 9.14%.

1d, yield 68%, mp 212–215 °C. ^{1}H-NMR 2.19 and 2.78 (2H, 2 × m, CH_2), 3.98 (2H, m, NCH_2), 5.07 (1H, t, J = 9.0, SCH), 7.31 (1H, m, Ar H-6), 7.49 (1H, t, J = 8.1, Ar H-5), 7.62 (1H, m, Ar H-4), 7.88 (1H, t, J = 2.0, Ar H-2), 9.26 and 9.46 (4H, 2 × br s, 2 × NH_2); ^{13}C-NMR 24.5 (CH_2), 45.9 (S–CH), 46.7 (NCH_2),

118.4 (Ar C-6), 119.7 (Ar C-2), 125.0 (Ar C-3), 130.7 (Ar C-4), 133.4 (Ar C-5), 140.0 (Ar C-1), 168.6 (C=N), 170.5 (C=O).

Anal. C, 37.84; H, 3.81; N, 11.81; S, 9.07. $C_{11}H_{13}BrClN_3OS$ requires C, 37.68; H, 3.74; N, 11.98; S, 9.14%.

1e, yield 76%, mp 183–185 °C. ^{1}H-NMR 2.22 and 2.81 (2H, 2 × m, CH_2), 4.03 (2H, m, NCH_2), 5.10 (1H, t, J = 9.1, SCH), 7.60 (1H, dd, J = 8.4 and 0.6, Ar H-4), 7.71 (1H, t, J = 8.0, Ar H-5), 7.89 (1H, dd, J = 8.2 and 1.6, Ar H-6), 8.20 (1H, s, Ar H-2), 9.26 and 9.47 (4H, 2 × br s, 2 × NH_2); ^{13}C-NMR 24.5 (CH_2), 45.9 (S–CH), 46.7 (NCH_2), 116.5 (Ar C-2), 121.5 (Ar C-4), 123.6 (Ar C-6), 124.0 (q, J = 273, CF_3), 129.6 (q, J = 32, Ar C-3), 130.3 (Ar C-5), 139.3 (Ar C-1), 168.6 (C=N), 170.8 (C=O).

Anal. C, 37.64; H, 3.52; N, 10.86; S, 8.21. $C_{12}H_{13}BrF_3N_3OS$ requires C, 37.51; H, 3.41; N, 10.94; S, 8.34%.

1f, yield 84%, mp 235–238 °C. ^{1}H-NMR 2.23 and 2.82 (2H, 2 × m, CH_2), 4.07 (2H, m, NCH_2), 5.05 (1H, t, J = 9.1, SCH), 7.78 (1H, t, J = 8.2, Ar H-5), 8.03 (1H, dd, J = 8.2 and 2.0, Ar H-4), 8.11 (1H, dd, J = 8.2 and 2.0, Ar H-6), 8.74 (1H, t, J = 2.1, Ar H-2), 9.25 and 9.43 (4H, 2 × br s, 2 × NH_2); ^{13}C-NMR 24.4 (CH_2), 45.8 (S–CH), 46.7 (NCH_2), 114.4 (Ar C-2), 119.6 (Ar C-2), 125.9 (Ar C-6), 130.6 (Ar C-5), 139.6 (Ar C-1), 148.0 (Ar C-3), 168.5 (C=N), 171.0 (C=O).

Anal. C, 36.64; H, 3.70; Br, 21.99; N, 15.45; S, 8.79. $C_{11}H_{13}BrN_4O_3S$ requires C, 36.58; H, 3.63; Br, 22.12; N, 15.51; S, 8.88%.

1g, yield 81%, mp 225–228 °C. ^{1}H-NMR 2.20 and 2.78 (2H, 2 × m, CH_2), 4.01 (2H, m, NCH_2), 5.11 (1H, t, J = 9.1, SCH), 7.93 (4H, 2 × AA′XX′, Ar H-2,3,5,6), 9.27 and 9.43 (4H, 2 × br s, 2 × NH_2); ^{13}C-NMR 24.4 (CH_2), 45.9 (S–CH), 46.4 (NCH_2), 106.8 (Ar C-4), 118.7 (CN), 119.9 (Ar C-2,6), 133.2 (Ar C-3,5), 142.5 (Ar C-1), 168.5 (C=N), 170.9 (C=O).

Anal. C, 42.32; H, 3.92; Br, 23.34; N, 16.31; S, 9.31. $C_{12}H_{13}BrN_4OS$ requires C, 42.24; H, 3.84; Br, 23.42; N, 16.42; S, 9.40%.

3b, yield 64%, mp 165–167 °C. ^{1}H-NMR 2.17 and 2.77 (2H, 2 × m, CH_2), 3.00 (3H, s, NCH_3), 3.99 (2H, m, NCH_2), 5.04 (1H, t, J = 8.8, SCH), 7.27 (1H, t, J = 7.4, Ar H-4), 7.47 (2H, t, J = 7.6, Ar H-3,5), 7.70 (2H, d, J = 7.8, Ar H-2,6), 9.35 and 9.71 (2H, 2 × br s, NH_2), 10.02 (1H, br s, NH); ^{13}C-NMR 24.4 (CH_2), 30.9 (NCH_3), 46.3 (S–CH), 46.8 (NCH_2), 120.2 (Ar C-2,6), 125.4 (Ar C-4), 129.0 (Ar C-3,5), 138.6 (Ar C-1), 165.1 (C=N), 170.5 (C=O).

Anal. C, 43.75; H, 4.94; Br, 24.06; N, 12.64; S, 9.59. $C_{12}H_{16}BrN_3OS$ requires C, 43.64; H, 4.88; Br, 24.20; N, 12.72; S, 9.71%.

3c, yield 71%, mp 211–213 °C. ^{1}H-NMR 2.17 and 2.76 (2H, 2 × m, CH_2), 3.00 (3H, s, NCH_3), 3.98 (2H, m, NCH_2), 5.07 (1H, t, J = 8.9, SCH), 7.54 (2H, AA′XX′, J = 9.0, Ar H-3,5), 7.75 (2H, AA′XX′, J = 8.9, Ar H-2,6), 9.35 and 9.68 (2H, 2 × br s, NH_2), 10.00 (1H, br s, NH); ^{13}C-NMR 24.3 (CH_2), 31.0 (NCH_3), 46.2 (S–CH), 46.7 (NCH_2), 121.7 (Ar C-2,6), 128.9 (Ar C-3,5), 129.1 (Ar C-4), 137.5 (Ar C-1), 165.0 (C=N), 170.5 (C=O).

Anal. C, 39.66; H, 4.27; N, 11.44; S, 8.65. $C_{12}H_{15}BrClN_3OS$ requires C, 39.52; H, 4.15; N, 11.52; S, 8.79%.

3d, yield 75%, mp 170–172 °C. ^{1}H-NMR 2.14 and 2.77 (2H, 2 × m, CH_2), 3.00 (3H, s, NCH_3), 3.97 (2H, m, NCH_2), 5.17 (1H, t, J = 8.9, SCH), 7.30 (1H, m, Ar H-6), 7.48 (1H, t, J = 8.1, Ar H-5), 7.60 (1H, m, Ar H-4), 7.87 (1H, br s, Ar H-2), 9.38 and 9.70 (2H, 2 × br s, NH_2), 10.01 (1H, br s, NH); ^{13}C-NMR 24.4 (CH_2), 31.0 (NCH_3), 46.3 (S–CH), 46.7 (NCH_2), 118.4 (Ar C-6), 119.7 (Ar C-2), 124.9 (Ar C-3), 130.6 (Ar C-4), 133.3 (Ar C-5), 139.9 (Ar C-1), 164.9 (C=N), 170.6 (C=O).

Anal. C, 39.62; H, 4.19; N, 11.47; S, 8.70. $C_{12}H_{15}BrClN_3OS$ requires C, 39.52; H, 4.15; N, 11.52; S, 8.79%.

3e, yield 84%, mp 166–168 °C. ^{1}H-NMR 2.21 and 2.80 (2H, 2 × m, CH_2), 3.00 (3H, s, NCH_3), 4.05 (2H, dd, J = 8.1 and 5.4, NCH_2), 5.06 (1H, t, J = 8.9, SCH), 7.62 (1H, m, Ar H-4), 7.73 (1H, t, J = 7.9, Ar H-5), 7.90 (1H, m, Ar H-6), 8.21 (1H, br s, Ar H-2), 9.38 and 9.70 (2H, 2 × br s, NH_2), 9.98 (1H, br s, NH); ^{13}C-NMR 24.3 (CH_2), 31.0 (NCH_3), 46.2 (S–CH), 46.7 (NCH_2), 116.4 (q, J = 3.9, Ar C-2), 121.5 (q, J = 4.0, Ar C-4) 123.6 (Ar C-6), 124.1 (q, J = 272, CF_3), 129.6 (q, J = 32, Ar C-3), 130.3 (Ar C-5), 139.3 (Ar C-1), 164.9 (C=N), 170.9 (C=O).

Anal. C, 39.28; H, 3.84; N, 10.50; S, 7.98. $C_{13}H_{15}BrF_3N_3OS$ requires C, 39.21; H, 3.80; N, 10.55; S, 8.05%.

3f, yield 81%, mp 181–184 °C. ^{1}H-NMR 2.21 and 2.80 (2H, 2 × m, CH_2), 3.00 (3H, s, NCH_3), 4.06 (2H, m, NCH_2), 5.03 (1H, t, J = 9.0, SCH), 7.78 (1H, t, J = 8.2, Ar H-5), 8.03 (1H, dd, J = 8.2 and 2.0, Ar H-4), 8.11 (1H, dd, J = 8.2 and 2.0, Ar H-6), 8.75 (1H, t, J = 2.1, Ar H-2), 9.38 and 9.64 (2H, 2 × br s, NH_2), 9.97 (1H, br s, NH); ^{13}C-NMR 24.3 (CH_2), 31.0 (NCH_3), 46.3 (S–CH), 46.7 (NCH_2), 114.4 (Ar C-2), 119.6 (Ar C-2), 125.9 (Ar C-6), 130.6 (Ar C-5), 139.6 (Ar C-1), 148.0 (Ar C-3), 164.9 (C=N), 171.1 (C=O).

Anal. C, 38.52; H, 4.10; Br, 21.12; N, 14.84; S, 8.48. $C_{12}H_{15}BrN_4O_3S$ requires C, 38.41; H, 4.03; Br, 21.29; N, 14.93; S, 8.54%.

3g, yield 74%, mp 198–201 °C. ^{1}H-NMR 2.21 and 2.79 (2H, 2 × m, CH_2), 4.02 (2H, m, NCH_2), 5.09 (1H, t, J = 8.9, SCH), 7.94 (4H, 2 × AA′XX′, Ar H-2,3,5,6), 9.36 and 9.65 (2H, 2 × br s, NH_2), 9.98 (1H, br s, NH); ^{13}C-NMR 24.3 (CH_2), 31.0 (NCH_3), 46.3 (S–CH), 46.4 (NCH_2), 106.9 (Ar C-4), 118.8 (CN), 119.9 (Ar C-2,6), 133.3 (Ar C-3,5), 142.5 (Ar C-1), 164.8 (C=N), 171.1 (C=O).

Anal. C, 44.03; H, 4.31; Br, 22.32; N, 15.69; S, 8.89. $C_{13}H_{15}BrN_4OS$ requires C, 43.95; H, 4.26; Br, 22.49; N, 15.77; S, 9.02%.

2-Imino-5-[2-(phenylamino)ethyl]thiazolidin-4-ones 2b–g and 4b–g

2b, yield 52%, mp 147–149 °C. ^{1}H-NMR 1.88 and 2.37 (2H, 2 × m, CH_2), 3.15 (2H, m, NCH_2), 4.34 (1H, dd, J = 9.8 and 3.8, SCH), 5.74 (1H, t, J = 5.6, Ar-NH), 6.56–6.61 (3H, m, Ar H-2,4,6), 7.11 (2H, t, J = 7.3, Ar H-3,5), 8.85 (1H, br s, NH), 9.05 (1H, br s, NH); ^{13}C-NMR 33.0 (CH_2), 41.6 (NCH_2), 54.4 (S–CH), 112.1 (Ar C-2,6), 115.9 (Ar C-4), 129.0 (Ar C-3,5), 148.7 (Ar C-1), 181.8 (C=N), 189.9 (C=O).

Anal. C, 56.26; H, 5.64; N, 17.78; S, 13.55. $C_{11}H_{13}N_3OS$ requires C, 56.15; H, 5.57; N, 17.86; S, 13.62%.

2c yield 59%, mp 167–169 °C. ^{1}H-NMR 1.86 and 2.34 (2H, 2 × m, CH_2), 3.16 (2H, m, NCH_2), 4.32 (1H, dd, J = 9.7 and 3.8, SCH), 6.59 (2H, AA′XX′, J = 8.7, Ar-H-2,6), 7.13 (2H, AA′XX′, J = 8.7, Ar-H-3,5), 8.84 (1H, br s, NH), 9.05 (1H, br s, NH); ^{13}C-NMR 30.8 (CH_2), 41.6 (NCH_2), 54.3 (S–CH), 113.5 (Ar C-2,6), 119.1 (Ar C-4), 128.7 (Ar C-3,5), 147.6 (Ar C-1), 181.7 (C=N), 189.8 (C=O).

Anal. C, 49.05; H, 4.40; Cl, 13.02; N, 15.61; S, 11.94. $C_{11}H_{12}ClN_3OS$ requires C, 48.98; H, 4.48; Cl, 13.14; N, 15.58; S, 11.89%.

2d, yield 54%, mp 159–161 °C. ^{1}H-NMR 1.88 and 2.34 (2H, 2 × m, CH_2), 3.16 (2H, m, NCH_2), 4.32 (1H, dd, J = 9.8 and 3.9, SCH), 6.12 (1H, t, J = 5.7, Ar-NH), 6.53–6.57 (2H, m, Ar H-4,6), 6.60 (1H, t, J = 2.1, Ar H-2), 7.11 (1H, t, J = 8.0, Ar H-5), 8.85 (1H, br s, NH), 9.05 (1H, br s, NH); ^{13}C-NMR 32.7 (CH_2), 41.4 (NCH_2), 54.3 (S–CH), 110.8 (Ar C-6), 111.2 (Ar C-2), 115.2 (Ar C-4), 130.5 (Ar C-5), 133.8 (Ar C-3), 150.1 (Ar C-1), 181.7 (C=N), 189.8 (C=O).

Anal. C, 48.91; H, 4.46; Cl, 13.10; N, 15.65; S, 11.96. $C_{11}H_{12}ClN_3OS$ requires C, 48.98; H, 4.48; Cl, 13.14; N, 15.58; S, 11.89%.

2e, yield 61%, mp 121–123 °C. ^{1}H-NMR 1.90 and 2.36 (2H, 2 × m, CH_2), 3.21 (2H, m, NCH_2), 4.35 (1H, dd, J = 9.7 and 3.8, SCH), 6.30 (1H, t, J = 5.6, Ar-NH), 6.82–6.85 (3H, m, Ar H-2,4,6), 7.31 (1H, t, J = 8.3, Ar H-5), 8.89 (1H, br s, NH), 9.07 (1H, br s, NH); ^{13}C-NMR 32.8 (CH_2), 41.3 (NCH_2), 54.4 (S–CH), 107.9 (q, J = 3.5, Ar C-2), 111.8 (q, J = 3.6, Ar C-4), 115.5 (Ar C-6), 124.7 (q, J = 272, CF_3), 130.0 (q, J = 31,

Ar C-3), 130.2 (Ar C-5), 149.2 (Ar C-1), 181.9 (C=N), 189.9 (C=O).

Anal. C, 47.64; H, 4.06; N, 13.77; S, 10.47. $C_{12}H_{12}F_3N_3OS$ requires C, 47.52; H, 3.99; N, 13.85; S, 10.57%.

2f, yield 67%, mp 201–203 °C. ^{1}H-NMR 1.92 and 2.38 (2H, 2 × m, CH_2), 3.24 (2H, m, NCH_2), 4.35 (1H, dd, J = 9.7 and 3.9, SCH), 6.55 (1H, t, J = 5.6, Ar-NH), 7.01 (1H, m, Ar H-6), 7.35–7.40 (3H, m, Ar H-2,4,5), 8.98 (2H, vbr s, 2 × NH); ^{13}C-NMR 32.7 (CH_2), 41.4 (NCH_2), 54.3 (S–CH), 105.4 (Ar C-2), 110.1 (Ar C-4), 118.4 (Ar C-6), 130.2 (Ar C-5), 149.1 (Ar C-3), 149.7 (Ar C-1), 181.8 (C=N), 189.9 (C=O).

Anal. C, 47.12; H, 4.29; N, 20.06; S, 11.50. $C_{11}H_{12}N_4O_3S$ requires C, 47.14; H, 4.32; N, 19.99; S, 11.44%.

2g, yield 60%, mp 209–211 °C. ^{1}H-NMR 1.91 and 2.34 (2H, 2 × m, CH_2), 3.23 (2H, m, NCH_2), 4.32 (1H, dd, J = 9.6 and 3.9, SCH), 6.66 (2H, AA′XX′, J = 8.6, Ar H-2,6), 6.85 (1H, br s, Ar-NH), 7.49 (2H, AA′XX′, J = 8.6, Ar H-3,5), 8.87 (1H, br s, NH), 9.07 (1H, br s, NH); ^{13}C-NMR 32.6 (CH_2), 40.8 (NCH_2), 54.1 (S–CH), 95.8 (Ar C-4), 111.9 (Ar C-2,6), 120.7 (CN), 133.5 (Ar C-3,5), 152.2 (Ar C-1), 181.1 (C=N), 189.6 (C=O).

Anal. C, 55.44; H, 4.72; N, 21.43; S, 12.19. $C_{12}H_{12}N_4OS$ requires C, 55.37; H, 4.65; N, 21.52; S, 12.32%.

4b, yield 50%, mp 127–129 °C. ^{1}H-NMR 1.88 and 2.37 (2H, 2 × m, CH_2), 2.93 and 2.99 and 3.00 (3H, 3 × s, NCH_3), 3.15 (2H, m, NCH_2), 4.34 (1H, m, SCH), 5.73 (1H, t, J = 5.6, Ar-NH), 6.56–6.61 (3H, m, Ar H-2,4,6), 7.11 (2H, t, J = 7.3, Ar H-3,5), 9.05 and 9.20 (1H, 2 × br s, NH); ^{13}C-NMR 31.1 (CH_2), 33.0 (NCH_3), 41.6 (NCH_2), 53.9 (S–CH), 112.2 (Ar C-2,6), 116.0 (Ar C-4), 129.1 (Ar C-3,5), 148.7 (Ar C-1), 179.6 (C=N), 189.1 (C=O).

Anal. C, 57.86; H, 6.10; N, 16.91; S, 12.83. $C_{12}H_{15}N_3OS$ requires C, 57.81; H, 6.06; N, 16.85; S, 12.86%.

4c, yield 53%, mp 162–165 °C. ^{1}H-NMR 1.86 and 2.34 (2H, 2 × m, CH_2), 2.92 and 2.98 and 3.06 (3H, 3 × s, NCH_3), 3.12 (2H, m, NCH_2), 4.33 (1H, m, SCH), 5.97 (1H, t, J = 5.6, Ar-NH), 6.59 (2H, AA′XX′, J = 8.8, Ar H-2,6), 7.12 (2H, AA′XX′, J = 8.8, Ar H-3,5), 9.20 and 9.55 (1H, 2 × br s, NH); ^{13}C-NMR 31.0 (CH_2), 32.8 (NCH_3), 41.6 (NCH_2), 53.8 (S–CH), 113.5 (Ar C-2,6), 119.1 (Ar C-4), 128.8 (Ar C-3,5), 147.6 (Ar C-1), 179.6 (C=N), 189.1 (C=O).

Anal. C, 50.85; H, 5.03; Cl, 12.53; N, 14.72; S, 11.24. $C_{12}H_{14}ClN_3OS$ requires C, 50.79; H, 4.97; Cl, 12.49; N, 14.81; S, 11.30%.

4d, yield 60%, mp 140–143 °C. ^{1}H-NMR 1.88 and 2.35 (2H, 2 × m, CH_2), 2.93 and 2.99 and 3.00 (3H, 3 × s, NCH_3), 3.16 (2H, m, NCH_2), 4.33 (1H, m, SCH), 6.13 (1H, t, J = 5.7, Ar-NH), 6.53–6.61 (3H, m, Ar H-2,4,6), 7.11 (1H, dt, J = 8.0 and 2.4, Ar H-5), 9.05 and 9.22 (1H, 2 × br s, NH); ^{13}C-NMR 31.0 (CH_2), 32.8 (NCH_3), 41.3 (NCH_2), 53.7 (S–CH), 110.8 (Ar C-6), 111.2 (Ar C-2), 115.2 (Ar C-4), 130.5 (Ar C-5), 133.8 (Ar C-3), 150.1 (Ar C-1), 179.4 (C=N), 189.0 (C=O).

Anal. C, 50.82; H, 5.00; Cl, 12.49; N, 14.81; S, 11.30. $C_{12}H_{14}ClN_3OS$ requires C, 50.79; H, 4.97; Cl, 12.49; N, 14.81; S, 11.30%.

4e, yield 57%, mp 137–139 °C. ^{1}H-NMR 1.91 and 2.37 (2H, 2 × m, CH_2), 2.93 and 2.99 and 3.05 (3H, 3 × s, NCH_3), 3.22 (2H, m, NCH_2), 4.36 (1H, m, SCH), 6.31 (1H, t, J = 5.5, Ar-NH), 6.84–6.87 (3H, m, Ar H-2,4,6), 7.32 (1H, t, J = 8.2, Ar H-5), 9.22 (1H, br s, NH); ^{13}C-NMR 31.1 (CH_2), 32.7 (NCH_3), 41.3 (NCH_2), 53.7 (S–CH), 107.9 (Ar C-2), 111.7 (C-4), 115.4 (Ar C-6), 124.7 (q, J = 272, CF_3), 129.8 (q, J = 21, Ar C-3), 130.1 (Ar C-5), 149.1 (Ar C-1), 179.5 (C=N), 189.0 (C=O).

Anal. C, 49.15; H, 4.50; N, 13.16; S, 10.03. $C_{13}H_{14}F_3N_3OS$ requires C, 49.21; H, 4.45; N, 13.24; S, 10.10%.

4f, yield 72%, mp 175–177 °C. ^{1}H-NMR 1.92 and 2.38 (2H, 2 × m, CH_2), 2.93 and 2.99 and 3.04 (3H, 3 × s, NCH_3), 3.25 (2H, m, NCH_2), 4.36 (1H, dd, J = 9.6 and 3.9, SCH), 6.56 (1H, t, J = 5.4, Ar-NH), 7.02 (1H, m, Ar H-6), 7.35–7.40 (3H, m, Ar H-2,4,5), 9.22 (1H, br s, NH); ^{13}C-NMR 31.2 (CH_2), 32.7 (NCH_3), 41.5 (NCH_2), 53.8 (S–CH), 105.5 (Ar C-2), 110.2 (Ar C-4), 118.5 (Ar C-6), 130.3 (Ar C-5), 149.1 (Ar C-3), 149.8 (Ar C-1), 179.6 (C=N), 189.1 (C=O).

Anal. C, 49.03; H, 4.86; N, 18.97; S, 10.75. $C_{12}H_{14}N_4O_3S$ requires C, 48.97; H, 4.79; N, 19.04; S, 10.89%.

4g, yield 62%, mp 163–165 °C. ^{1}H-NMR 1.91 and 2.35 (2H, 2 × m, CH_2), 2.92 and 2.98 and 3.04 (3H, 3 × s, NCH_3), 3.24 (2H, m, NCH_2), 4.34 (1H, dd, J = 9.6 and 3.9, SCH), 6.66 (2H, AA′XX′, J = 8.6, Ar H-2,6), 6.85 (1H, t, J = 5.3, Ar-NH), 7.49 (2H, AA′XX′, J = 8.6, Ar H-3,5), 9.22 and 9.70 (1H, 2 × br s, NH); ^{13}C-NMR 31.1 (CH_2), 32.6 (NCH_3), 40.9 (NCH_2), 53.6 (S–CH), 96.0 (Ar C-4), 112.0 (Ar C-2,6), 120.8 (CN), 133.6 (Ar C-3,5), 152.1 (Ar C-1), 179.5 (C=N), 189.0 (C=O).

Anal. C, 57.00; H, 5.22; N, 20.37; S, 11.66. $C_{13}H_{14}N_4OS$ requires C, 56.92; H, 5.14; N, 20.42; S, 11.69%.

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