Synthesis of novel mesoionic [1,2,4]triazolo[1,5-*a*] pyridin-4-ium-2-thiolates with antibacterial activity

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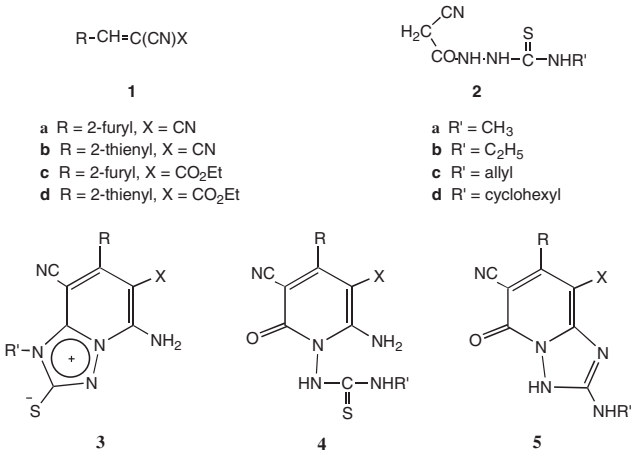
The [1,2,4]triazolo[1,5-*a*]pyridinium-2-thiolates **3a–n** and triazolo-pyridinium iodides **11a–g** have been synthesised and characterised. A number of the newly synthesised products were screened for *in vitro* antibacterial activity.

Keywords: fused pyridines, fused 1,2,4-triazoles, mesoionic compounds, antibacterials

Mesoionic betaines are well known as useful synthetic intermediates in the synthesis of a variety of heterocyclic biologically active compounds. [1,2,4]triazolo[4,3-*a*]pyridines[4] have been often found in various biologically active compounds and functional materials.[5] Also, some derivatives of triazolo [4,5-*c*]pyridinium bromides were reported for their significant antimicrobial activity.[8] In the course of the attempted synthesis of a series of thioureido-pyridones (**4**) we discovered that mesoionic cyclic products were usually obtained. This observation led to the synthesis and antibacterial screening of some novel mesoionic substituted [1,2,4]triazolo[1,5-*a*]pyridinium-2-thiolates and related derivatives which are described in this paper.

Thus, upon reacting **1a–d** with the cyanoacetic hydrazides **2a–d** in the presence of triethylamine, the 1,7-disubstituted 5-amino-6,8-dicyano-1*H*-[1,2,4]triazolo[1,5-*a*]pyridin-4-ium-2-thiolates **3a–f** and 5-amino-8-cyano-6-ethoxycarbonyl-1*H*-[1,2,4]triazolo[1,5-*a*]pyridin-4-ium-2-thiolates **3g–n** were afforded, rather than the expected thiourea[17] derivatives **4** or 2-(substituted amino)triazolopyridines **5**. However, reaction of **1a** and **b** with **2d** was found to afford 4-substituted 1-(6-amino-3,5-dicyano-2-oxo-2*H*-pyridin-1-yl)-3-cyclohexylthioureas (**4a**, R = 2-furyl; **b**, R = 2-thienyl; R' = C_6H_{11}; X = CN) (Scheme 1).



Scheme 1

Formation of products of type **3** could occur by Michael addition of **1** to **2** followed by cyclisation, aromatisation, and further cyclisation and dehydration as shown in Scheme 2. The infrared spectra of **3** were characterised by the presence of (C–S^-)[20] peaks at 1271–1292cm^{-1}.

The structure of products **3** was confirmed chemically by reaction with ethyl iodide. Upon reacting **3b**, **e**, **g**, **h**, **k–m** (selected examples) with ethyl iodide the anionic sulfur moieties were easily alkylated and afforded smoothly the 5-amino-2-ethylsulfanyl-1*H*-[1,2,4]triazolo[1,5-*a*]pyridin-4-ium iodide derivatives **11a–g** (Scheme 3). This contra-indicated the alternative structures **10** for the products **3**.

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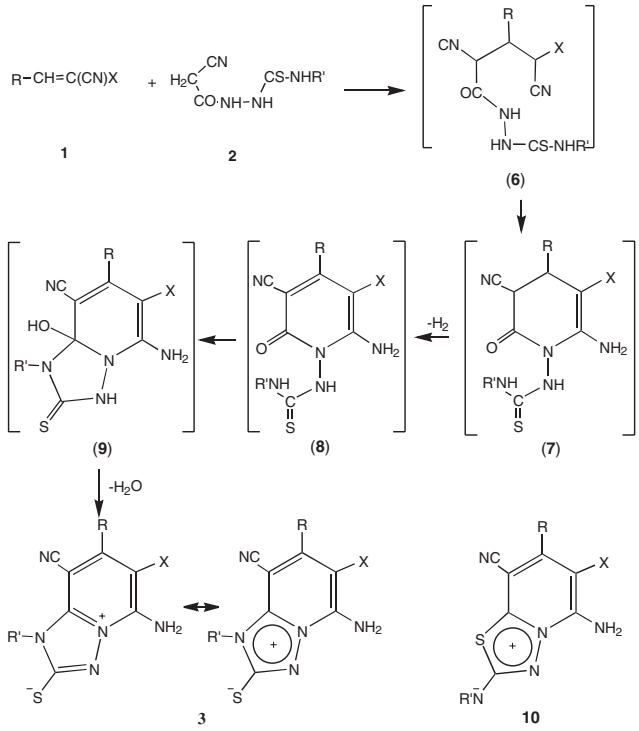
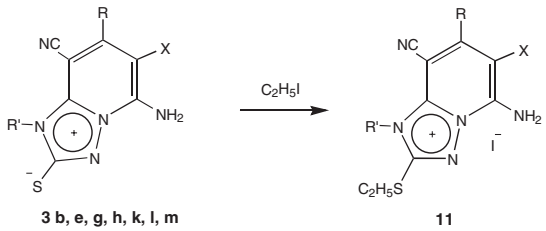


3	R	R'	X	3	R	R'	X
a	2-furyl	CH_3	CN	**h**	2-furyl	C_2H_5	CO_2Et
b	2-furyl	C_2H_5	CN	**i**	2-furyl	allyl	CO_2Et
c	2-furyl	allyl	CN	**j**	2-furyl	cyclohexyl	CO_2Et
d	2-thienyl	CH_3	CN	**k**	2-thienyl	CH_3	CO_2Et
e	2-thienyl	C_2H_5	CN	**l**	2-thienyl	C_2H_5	CO_2Et
f	2-thienyl	allyl	CN	**m**	2-thienyl	allyl	CO_2Et
g	2-furyl	CH_3	CO_2Et	**n**	2-thienyl	cyclohexyl	CO_2Et

Scheme 2



11	R	R'	X	11	R	R'	X
a	2-furyl	C_2H_5	CN	**e**	2-thienyl	CH_3	CO_2Et
b	2-thienyl	C_2H_5	CN	**f**	2-thienyl	C_2H_5	CO_2Et
c	2-furyl	CH_3	CO_2Et	**g**	2-thienyl	allyl	CO_2Et
d	2-furyl	C_2H_5	CO_2Et				

Scheme 3

The synthesised products **3a–f**, **h**, **i**, **k–m**, **4a**, **b** and **11b**, **c**, **f** and **g** were tested against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The observed activities of the tested compounds were compared with the activity of the antibiotic chloramphenicol against the same tested microorganisms. It was found that compounds **3b**, **e**, **f**, **4a** and **11c**, **f** showed significant activity towards all the tested micro-organisms.

Techniques used: IR, ^{1}H NMR, MS, antibacterial screening by disk diffusion method.

Schemes: 3

References: 25

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