Synthetic route to 4,5-dihydro-9*H*-pyrido[1,2-*a*] thieno[3,2-e]pyrimidine derivatives through 1,3-dipolar cycloaddition

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A synthetic route to the title heterocyclic system through 1,3-dipolar cycloaddition of the mesoionic compound **9** with DMAD is described. The structure elucidation of the above system is also reported.

Keywords: mesoionic rings, fused thiazoles, pyrimidines, pyridines, cycloaddition, extrusion

For many years we have been concerned with the synthesis and the pharmacological activity of derivatives containing the thieno[2,3-*d*]pyrimidin-4-one system linearly fused with diverse heterocyclic systems.[1–5] An exhaustive search through chemical literature showed that the thieno[2,3-*d*]pyrimidin-4-one system angularly fused [1,2-*a*] with the pyridine was obtained by Manhas *et al*.[6] and Kovtunenko *et al*.[7] as derivatives with the pyridine moiety partially hydrogenated and without functional groups. In this paper, we report an alternative route for obtaining the above angular system with functional groups on the partially saturated pyridine.

The 3-amino-2,3-dihydro-5,6-dimethyl-2-thioxo-thieno[2,3-*d*]pyrimidin-4(1*H*)-one (**5**)[4,8] was used as a key intermediate, and its preparation was obtained through a series of reactions that improved the yields and avoided the production of pollutants in comparison with the previous preparations[4,8] (Scheme 1).

Dropwise addition at room temperature of a solution in acetone of ethyl 4,5-dimethyl-2-aminothiophene-3-carboxylic acid (**1**) in light molar excess to a stirred solution of thiophosgene in acetone and subsequent dilution with water, separated the ethyl ester of 4,5-dimethyl-2-isothiocyanatothiophene-3-carboxylic acid (**2**).[9] This isothiocyanate **2**, added dropwise at room temperature to a stirred solution in chloroform of hydrazine hydrate, formed the thiosemicarbazide derivative **3** that was cyclised to the sodium salt **4** by heating in presence of an equimolar quantity of sodium hydroxide dissolved in ethanol; by acidification of the above salt **4** in water with hydrochloric acid, the key amino-thioxo intermediate **5** was obtained. The analytical and spectral data of isothiocyanate **2** of amino-thioxo derivative **5** were identical with those reported in previous papers.[4,8,9] The reaction of amino-thioxo derivative **5** with triethyl orthobenzoate under appropriate conditions gave the 6,7-dimethyl-2-phenyl-8*H*-[1,3,4]thiadiazolo[3,2-*a*] thieno[2,3-*d*]pyrimidin-8-one (**6**), that proved to be identical to that obtained by Russo *et al*.[1] from the condensation of amino-ethyl ester **1** with 2-chloro-5-phenyl-1,3,4-thiadiazole. The synthesis of phenyl derivative **6** allowed us to propose the amino-thioxo structure for the key compound **5**, and to exclude alternative dimeric structures which may be oibtained, since hydrazine is a bifunctional regeant.

In a previous paper[5] we have reported that the mesoionic compound obtained from the above key intermediate **5**, under prolonged heating, rearranged owing to the presence of the free amino group. Therefore we have protected the amino group by the reaction of compound **5** with 2,5-dimethoxy-tetrahydrofuran in refluxing acetic acid to obtain the intermediate 2,3-dihydro-5,6-dimethyl-3-(1*H*-pyrrol-1-yl)-2-thioxothieno[2,3-d]pyrimidin-4(1*H*)-one (**7**). This thioxo derivative **7** reacted at room temperature in the presence of triethylamine with (±)-α-bromophenylacetic acid to give the acid derivative **8** which, treated in benzene at room temperature with a mixture of acetic anhydride and triethylamine (v/v 1:1), cyclised to give the mesoionic compound **9**.

According to our procedure the crude acid and mesoionic derivatives **8** and **9** were pure on TLC. Analytical and spectral data are in agreement with the proposed structure for compounds **8** and **9**; in particular, in the mass spectrum of the mesoionic derivative **9**, the molecular ion [M^+] is confirmed at *m/z* 393 (100%) and an intense signal at *m/z* 121 (95 %), attributable to the fragment [$PhCS^+$], corroborates the formation of a phenyl-substituted mesoionic thiazole ring. The presence of this intense fragment is confirmed in the mass spectra of compounds bearing the structural analogous phenyl-thiazole mesoionic ring system.[5,10–15]

The use of mesoionic ring systems for ring annulation is a well-established procedure, resulting in either five- or six-membered fused systems.[10,11,13,14,16] The mesoionic compound **9** contains a "masked" 1,3-thiocarbonyl ylide dipole which is reported to undergo ready reaction of 1,3-dipolar cycloaddition with dipolarophiles[10,11,13,16] such as DMAD.

From the reaction mixture of the mesoionic derivative **9** with an excess of DMAD in refluxing dry benzene, under our procedural conditions, we isolated only compound **10** (yield 40%). The structure of this new derivative of the expected 4,5-dihydro-9*H*-pyrido[1,2-*a*]thieno[3,2-*e*]pyrimidine heterocyclic system was established by mass spectrum ([M^+] *m/z* 503; 100%), elemental analysis, IR, ^{1}H-NMR and ^{13}C-NMR data. Considering that the thiophene ring could react with the dipolarophile[17] (although thiophene itself is relatively inert to Diels–Alder reactions[18]), and that there was sulfur extrusion, one of two structures, **10** or **11**, could be assigned. (Scheme 2).

The angular pyrido[1,2-*a*]pyrimidine structure of compound **10** was assigned based on the following considerations: the values of the ^{1}H shifts of the two methyl groups of the annulated product do not change significantly with respect to those of the precursor mesoionic compound **9**, therefore the two methyl groups remain on the thiophene moiety; the ^{1}H and ^{13}C shifts of the two methoxy groups stay in the intervals δ = 3.33–3.41 and 52.41–52.71, respectively, therefore the hydrogens and the carbons of the methoxy groups are all in similar environments; in the mass spectrum there is no fragment for *m/z* 121 attributable to the ion [$PhCS^+$] characteristic of the phenyl-substituted mesoionic thiazole ring, as the above.[5,10–15]

Moreover, Fischer *et al*.[14] have reported that the reaction of a thiazolo-thieno-pyridine derivative with an acetylenic dipolarophile gave a thieno-pyrido-pyridine derivative, without reacting with the thiophene moiety. However, in our case we were dealing with a dimethyl thiene-pyrimidine derivative.

Techniques used: IR, ^{1}H and ^{13}C NMR and elemental analysis, TLC mass spectrometry.

References: 18

Schemes: 2

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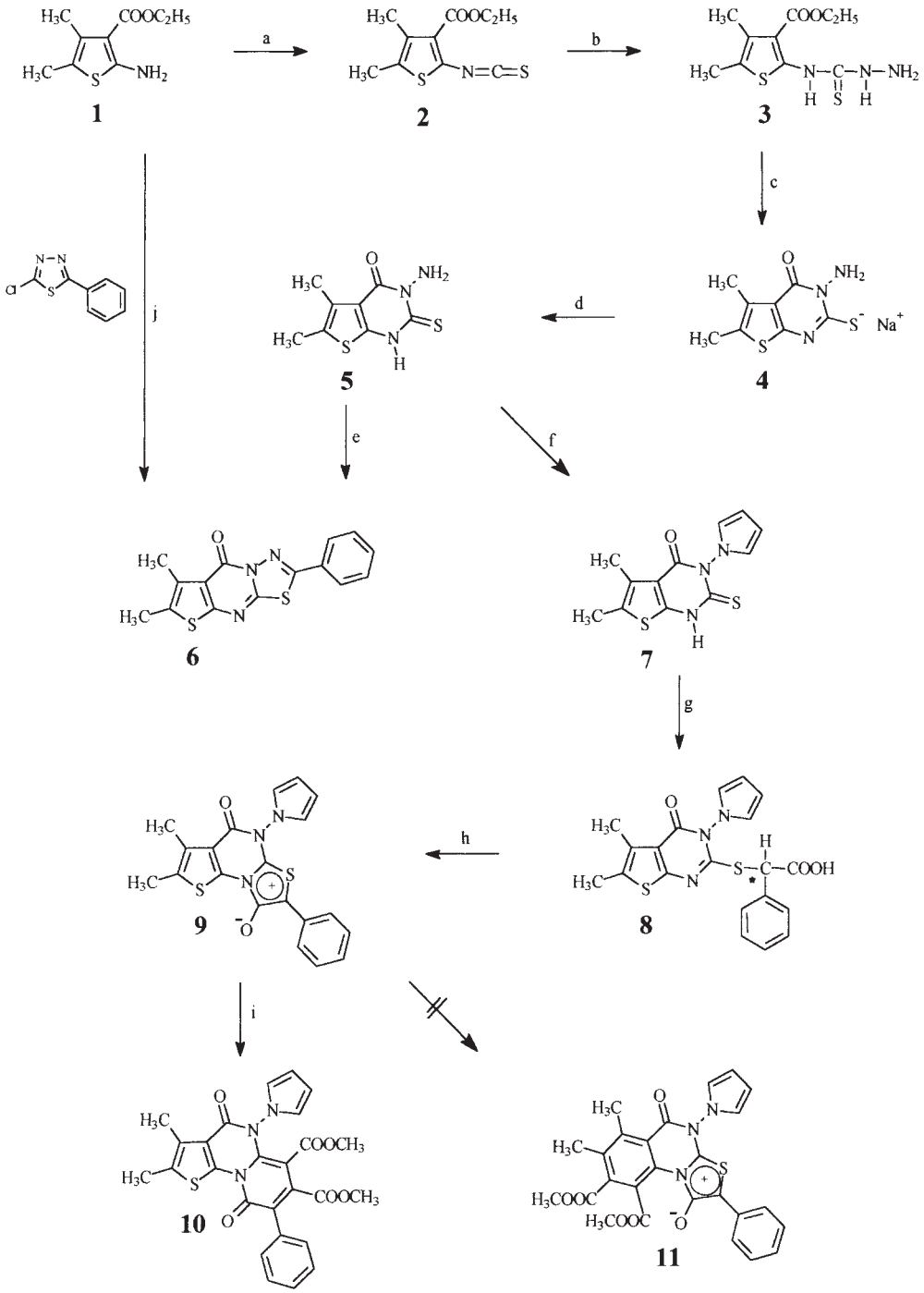

Scheme 1 Reagents and conditions: (a) Cl_2CS in CH_3COCH_3, rt, stirring 15 min/H_2O, 90%; (b) $NH_2NH_2{\cdot}H_2O$ in $CHCl_3$, rt, stirring 2 h, 75%; (c) NaOH in ethanol, reflux 30 min, 95%; (d) H_2O/HCl, rt, stirring 15 min, 95%; (e) triethyl orthobenzoate, 110°C, stirring 6 h, 40%; (f) 2,5-dimethoxytetrahydrofuran in CH_3COOH, reflux 3 h, 40%; (g) (±)α-bromophenylacetic acid in C_6H_6, Et_3N, rt, stirring 24 h / $NaHCO_3$, HCl, 50%; (h) Et_3N, Ac_2O in C_6H_6, rt, 2 h 70%; (i) DMAD in C_6H_6, reflux, 2 h, 40%; (j) Δ, 50%

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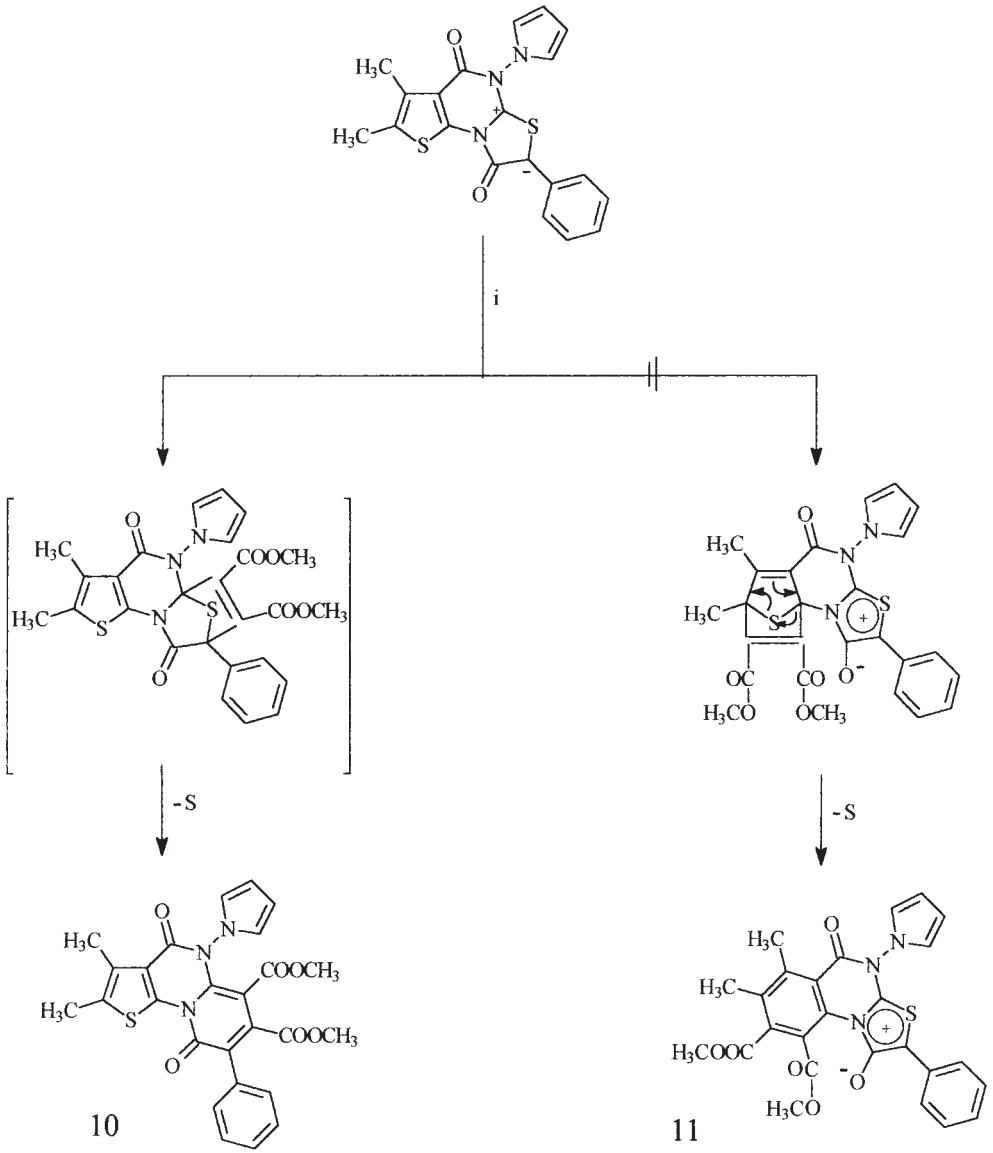

Scheme 2 Reagents and conditions: (i) DMAD in C_6H_6, reflux, 2 h, 40%

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