A facile route for the synthesis of thienopyrimidines

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Thieno[2,3-d]pyrimidines have been synthesized by a novel route via thieno[2,3-d]oxazinones which were in turn prepared by a facile single pot method.

Keywords: fused thiophenes, fused pyrimidines, fused 1,3-oxazin-4-ones

Several fused pyrimidinones with potentially useful pharmacological profiles such as antihistaminic,[1] and bronchodilation activities[2] has been reported. It has been established that the thiophene is a bioisostere of benzene in fused-ring systems.[3] The goal of the present investigation is to synthesise some new thienopyrimidinone derivatives for evaluation of their bronchodilator activity. While different synthetic routes to this ring system are known, the one involving the condensation of nitriles with 2-amino-3-thiophenecarboxylic esters catalysed by dry hydrogen chloride is the popular route.

We have developed an alternative and safer route for the synthesis of thienopyrimidinones, which avoids the use of hydrogen chloride gas. The required thieno-oxazinones (**2a–g**), previously obtained via lengthy routes,[16] were prepared by a reaction of 2-amino-3-thiophenecarboxylic acids[17] with acid anhydrides or benzoyl chloride.[18]

The NMR spectra of the compounds showed the absence of NH and of carboxylic protons and mass spectra revealed the molecular ion of dehydrated product. Ammonolysis of the thieno[2,3-*d*]oxazinones **(2)** gave 2-substituted 3,4-dihydro-4-oxothieno[2,3-*d*]pyrimidines (**3a–g**) in 50-60% yields. The formation of the products were indicated by a shift in the carbonyl signal in the IR spectrum from 1750 to 1650 cm^{-1} and an exchangeable (D_2O) NH signal in NMR spectra at δ 12. Furthermore, the mass spectra revealed the molecular ion appearing as a base peak. All the compounds were characterised based on their spectral data and elemental analyses. Yields and melting points of the products are listed in Table 1.

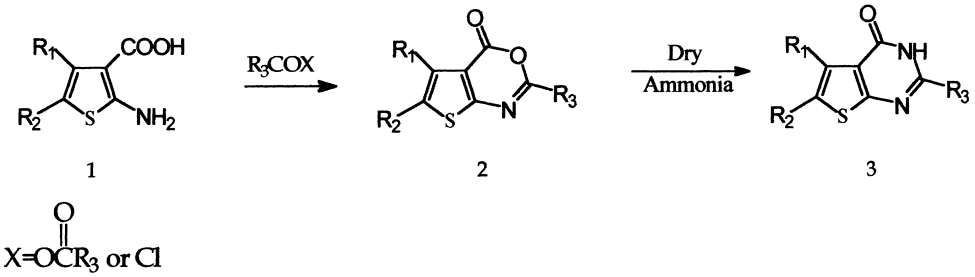
Techniques used: ^{1}H NMR, Mass spectrometry, IR.

References: 18

Schemes: 1

Table 1: Yields, melting points and elemental analyses of compounds **2–3**

Table 2: Mass and NMR spectral data of compounds **2-3**



1 2 3

a) $R_1 = R_2 = -(CH_2)_4-$, $R_3 = CH_3$ b) $R_1 = R_2 = R_3 = CH_3$ c) $R_1 = R_2 = -(CH_2)_4-$, $R_3 = C_2H_5$.

d) $R_1 = R_2 = CH_3$, $R_3 = C_2H_5$ e) $R_1 = R_2 = -(CH_2)_4-$, $R_3 = n\text{-}C_3H_7$ f) $R_1 = R_2 = CH_3$, $R_3 = -C_3H_7$.

g) $R_1 = R_2 = CH_3$, $R_3 = C_6H_5$

Scheme 1

Table 1 Yields and melting points of compounds **2–3**

Cmpd	Yield/%	m.p./°C	Cmpd	Yield/%	m.p./°C
2a	90	128–130[a]	**3a**	55	297–298[c]
2b	86	108–110[a]	**3b**	52	284–286[c]
2c	87	118–119	**3c**	58	232–234[d]
2d	89	86–88	**3d**	60	244–246
2e	85	90–91	**3e**	64	214–216
2f	80	82–84	**3f**	60	184–185
2g	85	136–138[b]	**3g**	68	294–295[c]

[a]Lit.[16a] m.p. **2a** 130–132°C; **2b** 104–105°C. [b]Lit.[16b] m.p. **2g** 140–142°C. [c]Lit.[9] m.p. **3a** 300–301°C; **3b** 286–288°C; **3g** 300–302°C. [d]Lit.[11] m.p. **3c** 253–254°C.

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