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Thiophenol mediated radical cyclization: an expedient approach to 2*H*-pyrrolo[3,2-*d*]pyrimidines (9-deazaxanthine analogs)

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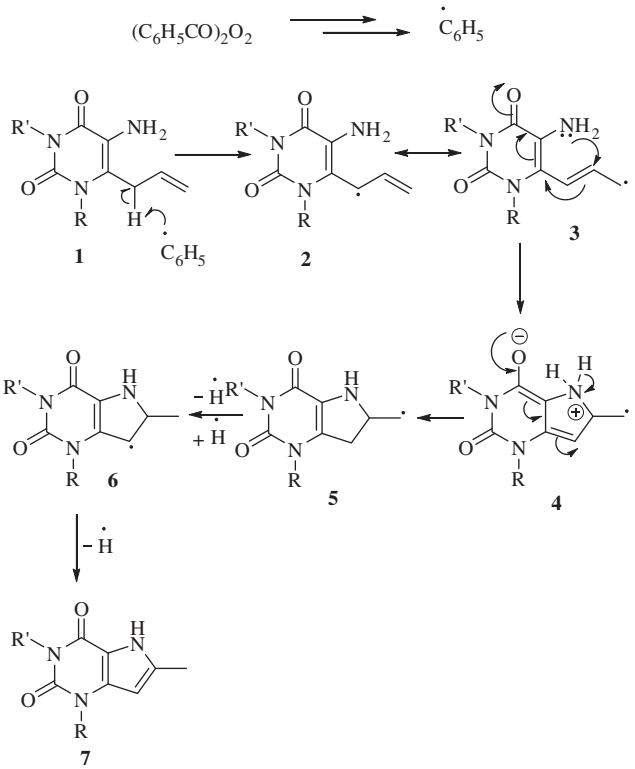
ABSTRACT

A new efficient route for the synthesis of substituted 2*H*-pyrrolopyrimidines (9-deazaxanthine analogs) via thiophenol mediated radical cyclization has been achieved. The stereochemistry of the newly synthesised compounds has been settled from NOE data.

Pyrimidines, being an integral part of DNA and RNA, exhibit diverse pharmacological properties as effective bactericides, fungicides, viricides, insecticides, and medicides.[1–3] Numerous pyrimidine and uracil-based molecules,[4] for example, 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxycytidine (DDC), (*E*)-5-[2-(bromovinyl)-2′-deoxyuridine] (BVDU), active against cancer and AIDS viruses,[5] have already been synthesised. Particularly, pyrrolo[3,2-*d*]pyrimidines (9-deazaxanthines) are important due to their proven biological activity and medicinal utility. 9-Deazaxanthines showed structure-activity relationships that are similar to those of xanthines. They were shown to be more or less equipotent to the corresponding xanthines at A2a adenosine receptors. 9-Deazaxanthines are generally at least 2–3-fold more potent than xanthines at A1 receptors and, therefore, exhibit higher A1 selectivities compared to the xanthines.[6] Moreover, pyrrolopyrimidine ring system has aroused considerable interest due to its presence in several natural products like toyocamycin, sangivamycin, tubercidin etc.[7,8]

On the other hand, free radical cyclization is regarded as a versatile route for the construction of carbocycles as well as heterocycles.[9] In particular; the formation of C–S bonds by the intermolecular addition of S-centerd radicals to π-systems is a major challenge in organic synthesis. Intermolecular addition of radicals to terminal alkynes offers an attractive strategy for the generation of alkenyl radicals[10] and thiophenol[11] is a very efficient reagent for this purpose. Moreover, during the cyclization process a phenylthio moiety is incorporated into the final cyclized products, which is



Scheme 1. Synthesis of 9-deazaxanthines by benzoyl peroxide mediated radical cyclization.

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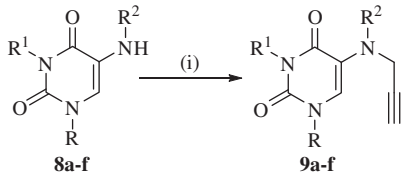


a, R = R^1 = R^2 = Me — **a,** R = R^1 = R^2 = Me, 95%
b, R = R^1 = Me, R^2 = Et — **b,** R = R^1 = Me, R^2 = Et, 93%
c, R = R^1 = Et, R^2 = Me — **c,** R = R^1 = Et, R^2 = Me, 91%
d, R = R^1 = R^2 = Et — **d,** R = R^1 = R^2 = Et, 90%
e, R = Et, R^1 = Me, R^2 = Me — **e,** R = Et, R^1 = Me, R^2 = Me, 92%
f, R = Et, R^1 = Me, R^2 = Et — **f,** R = Et, R^1 = Me, R^2 = Et, 94%

Scheme 2. Synthesis of precursors **9a–f**. Reagents and conditions: (i) propargyl bromide, K_2CO_3, acetone, reflux, 10–12 h.

particularly attractive for further transformation/functionalization.[11b,11c]

In our previous report[12] we have published a new synthetic route for the synthesis of substituted 9-deazaxanthines in excellent yields via aza-Claisen rearrangement followed by benzoyl peroxide mediated radical cyclization which is shown in Scheme 1.

Therefore, in continuation of our work in radical chemistry and the synthesis of biologically active heterocycles,[13] we became interested in the synthesis of novel pyrrolo[3,2-*d*]pyrimidine (9-deazaxanthine derivatives) via thiophenol mediated radical cyclization and herein we report our results.

The requisite starting materials for our study, **9a–f** were synthesised in 90–95% yield by refluxing various substituted 5-amino uracil derivatives **8a–f** and propargyl bromide in dry acetone-K_2CO_3 for 10–12 h. The amino uracil derivatives **8a-f** were in turn prepared from the bromouracil derivatives according to our earlier published procedure.[13g] The synthetic route of the aforesaid precursors is shown in Scheme 2.

The thiophenol mediated cyclization was then carried out with **9a** under standard conditions [PhSH (2 equiv), AIBN (1.5 equiv)] in dry benzene for 2 h to afford compound **10a** in only 30% yield along with the depropargylated product **8a** in 60% yield. Therefore to establish the optimized conditions of the radical cyclization we have performed a series of experiments where sequential changes were made to the radical initiator, amount of thiophenol and the solvent used. Very slow addition of PhSH (2 equiv) and use of AIBN (1.5 equiv) as radical initiator in refluxing *t*-butanol afforded the cyclized product **10a**[14] as a white solid, mp 114–116 °C in 65% yield along with some depropargylated product **8a** (25%). The optimization results are shown in Table 1.

The configuration of the exocyclic double bond in **10a** was found to be *trans* on the basis of only nOe correlation between

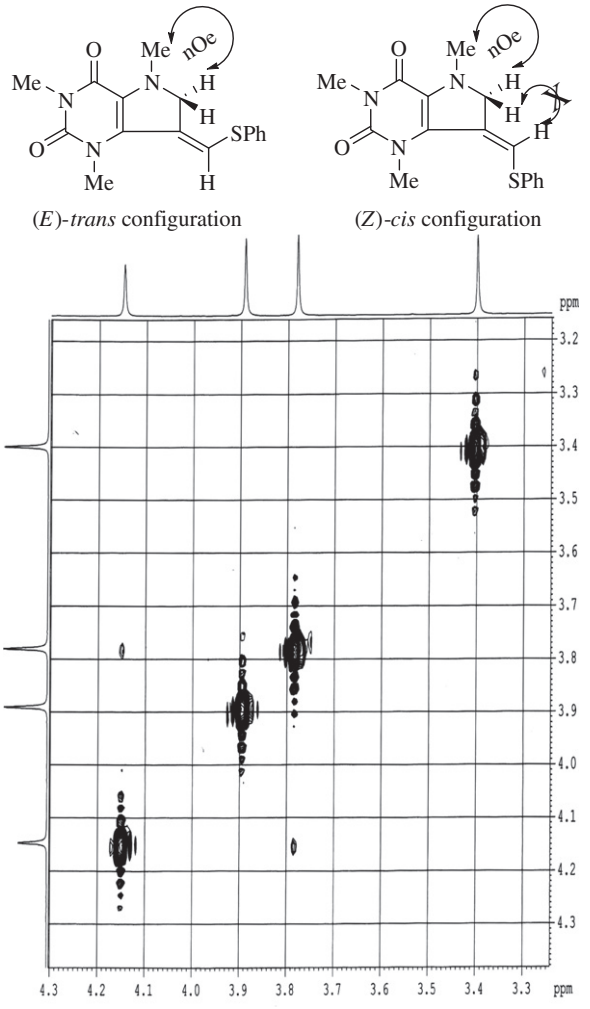


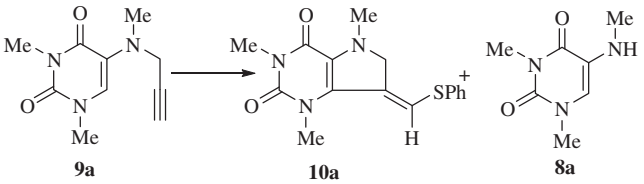
Figure 1. nOe of compound **10a**.

the methylene proton (–NCH_2) at δ = 4.15 ppm and the –N–CH_3 proton at δ = 3.79 ppm. There is no nOe correlation between the methylene proton (–NCH_2) at δ = 4.15 ppm with the exocyclic proton at δ = 6.63 ppm (Fig. 1).

Encouraged by this result, the other substrates **9b–f** were similarly treated to give **10b–f** in 60–63% yields. The results are summarized in Table 2.

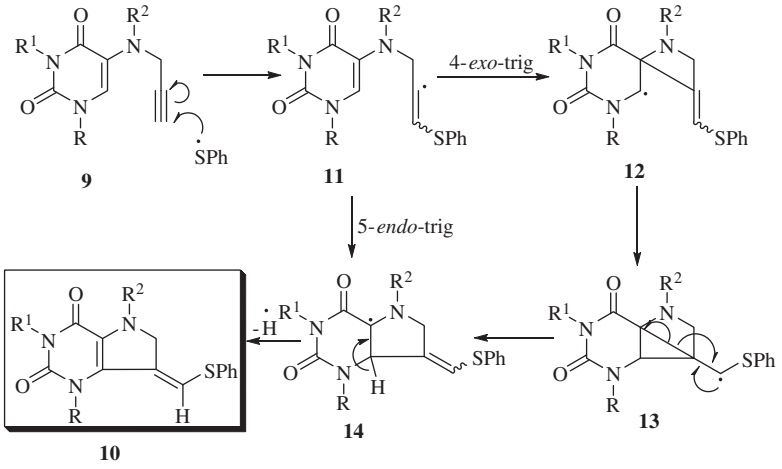
A probable mechanistic rationalization of the thiophenol mediated radical reaction is shown in Scheme 3. The formation

Table 1
Optimization of the radical cyclization of **9a**[a]



Entry	Reaction conditions	Time (h)	**10a** (%)	**8a** (%)
1	PhSH (2 equiv), AIBN (1.5 equiv), benzene, reflux	2	30	60
2	PhSH (2 equiv), benzoyl peroxide (1.5 equiv), benzene, reflux	1.5	—	65
3	PhSH (1.5 equiv), benzoyl peroxide (1.2 equiv), *t*-BuOH, reflux	1.5	30	30
4	PhSH (2 equiv), AIBN (1.5 equiv), *t*-BuOH, reflux	2	65	25
5	PhSH (4 equiv), AIBN (3 equiv), *t*-BuOH, reflux	2	62	25

[a] All the reactions were carried out under nitrogen atmosphere.

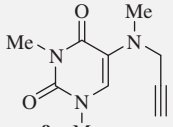
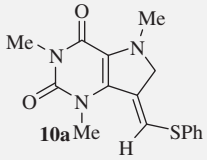
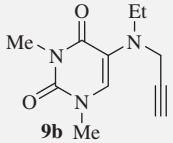
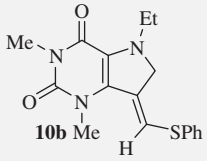
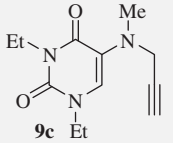
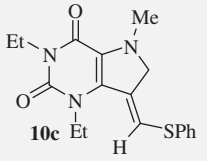
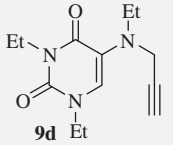
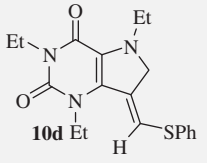
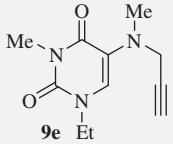
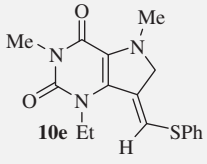
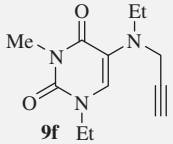
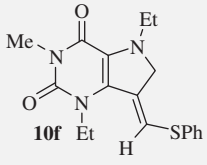


Scheme 3. Probable mechanistic path for the formation of 9-deazaxanthines **9**.

of the products **10** from **9** may be explained by the generation of alkenyl radical **11** by radical addition of thiophenol to the terminal alkyne **9**. The alkenyl radical **11** may undergo either a 4-*exo*-trig or a 5-*endo*-trig cyclization at the double bond of the uracil moiety. A 5-*endo*-trig cyclization of radical **11** may produce the intermediate radical **14**, while 4-*exo*-trig cyclization may give the spiroheterocyclic radical **12**, followed by neophyl rearrangement of **12** to radical intermediate **13**. Oxidative elimination of a hydrogen from **14** may afford **10**.

In conclusion, we have successfully achieved a practical method for the synthesis of 2*H*-pyrrolo[3,2-*d*]pyrimidine (9-deazaxanthine analogs) derivatives. We are continuing this work to extend the scope of this methodology to the synthesis of other bio-active heterocycles and the results will be communicated in due course.

Table 2
2*H*-Pyrrolo[3,2-*d*]pyrimidine derivatives

Entry	Precursors	Products	Yields (%)
1	 **9a**	 **10a**	65
2	 **9b**	 **10b**	62
3	 **9c**	 **10c**	60
4	 **9d**	 **10d**	63
5	 **9e**	 **10e**	61
6	 **9f**	 **10f**	60

Acknowledgments

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14. *General procedure for the synthesis of 2H-pyrrolo[3,2-d]pyrimidine derivatives* ***10*** *(****a****–****f****) by thiophenol-mediated radical cyclization*: A deoxygenated solution of thiophenol (0.97 mmol, 0.1 mL) in dry *t*-butanol (3 mL) was added dropwise to a solution of compound **9a** (0.48 mmol, 100 mg) and radical initiator AIBN (0.72 mmol, 119 mg) in refluxing anhydrous *t*-butanol (3 mL) under a nitrogen atmosphere for a period of 1 h and then the reaction mixture was further refluxed for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and stirred with saturated $NaHCO_3$ solution (10 mL) for 2 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with water (2 × 15 mL), brine solution (10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using 10% EtOAc/Pet. ether as eluent to afford the 2*H*-pyrrolo[3,2-*d*]pyrimidine derivative **10a** (99 mg, 65%) as a white solid. The other substrates **9** (**b**–**f**) were similarly treated to give products **10** (**b**–**f**). *Compound* **10a**: white solid, mp 114–116 °C; yield 65%. IR (KBr, cm^{-1}) ν_{max}: 1689, 1656; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.40 (3H, s, CONC*H*$_3$CO), 3.79 (3H, s, C*H*$_3$NCH$_2$–), 3.90 (3H, s, CONC*H*$_3$C), 4.15 (2H, s, NC*H*$_2$C), 6.63 (1H, s, =C*H*–), 7.23–7.31 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.9, 30.9, 31.9, 35.8, 103.9, 111.8, 127.1, 129.1, 130.6, 131.3, 132.4, 135.4, 152.0, 155.9; MS: *m*/*z* = 315 [M^+]. Anal. Calcd for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32. Found: C, 60.79; H, 5.61; N, 13.20.