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Iodine mediated an efficient and greener thiocyanation of aminopyrimidines by a modification of the Kaufmann's reaction

Ricaurte Rodríguez [a,*], Patricia Camargo [a], César A. Sierra [a], Carlos Y. Soto [a], Justo Cobo [b,*], Manuel Nogueras [b]

[a] Departamento de Química, Universidad Nacional de Colombia, Bogotá AA 14490, Colombia
[b] Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain

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ABSTRACT

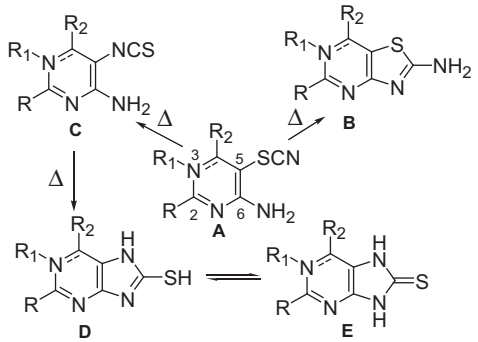
A new, safe, and efficient methodology for the thiocyanation of some aminopyrimidine derivatives has been implemented. The thiocyanation reactions proceeded at room temperature with high yields and selectivity. This route is a less toxic alternative to other common thiocyanation techniques because it uses molecular iodine as a halogen source, which is less reactive and easier to handle than chlorine or bromine.

From the synthetic point of view thiocyanation of aliphatic and aromatic organic compounds is a gateway to new kinds of organic molecules, which are very attractive for medicinal and organic synthetic chemists, as they can be transformed into a new class of compounds with a sulfur atom in their structures.

There is very little detailed experimental information about the synthesis of several thiocyanates of aminopyrimidine derivatives. The most common procedure, known as the Kaufmann methodology,[1] has several drawbacks. These issues include the employment of acetic acid or pyridine as a solvent, low temperature, excess of reagent, and the use of molecular chlorine or bromine, which are highly toxic and difficult to handle. Furthermore, in most of the cases, the reported yields under these reaction conditions are low as a result of complex reaction mixtures.[2]

On the other hand, there is a significant discrepancy regarding the results from the thiocyanation of some aminopyrimidines at the C-5 position. Baker and Chatfield reported the synthesis of compounds type **A**; while Maggiolo and Hitchings have claimed the synthesis of 2-aminothiazolo[4,5-*d*]pyrimidine derivatives (type **B**) occurring via an intermediate type **A**, under similar experimental conditions. At the same time, Maggiolo and Hitchings have reported that under heating thiocyanopyrimidine compounds (type **A**) can be transformed into isothiocyanopyrimidine derivatives type **C**.[2–4] Subsequently, it is possible that compounds (type **C**) can undergo an intramolecular nucleophilic attack to yield compounds type **D** and/or **E** (Scheme 1).

The controversial findings on the thiocyanation of some aminopyrimidine derivatives and the fact that there is not enough information available in the literature[5] about the structural characterization of the final products encourage us to find an optional synthetic methodology. So, in our continuing research program on the reactivity and transformation of aminopyrimidine derivatives into new compounds with attractive pharmacological activity,[6] we envisioned that molecular iodine, owing to its unique properties as nontoxic and easy to handle mild catalyst, can be used as a halogen source in the Kaufmann reaction.



Scheme 1. Possible transformations of thiocyanate derivative **A**.

* Corresponding authors. Tel.: +57 1 3165000; fax: +57 1 3165220 (R.R.).
E-mail addresses: rrodrigueza@unal.edu.co (R. Rodríguez), jcobo@ujaen.es (J. Cobo).

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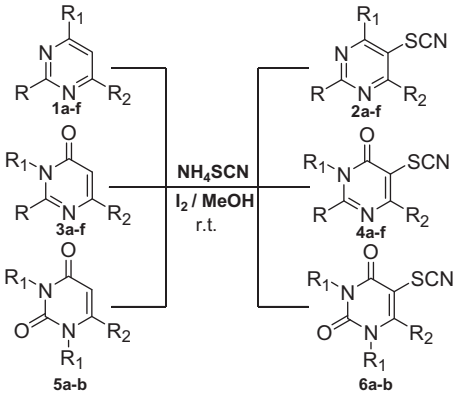


Scheme 2. Thiocyanation of some aminopyrimidine derivatives.

We report here a green, practical, and efficient methodology for the thiocyanation of some aminopyrimidine derivatives without any ambiguity, using molecular iodine to promote the reaction and methanol as a solvent at room temperature.[7] To the best of our knowledge, this is the first time that iodine is used in a Kaufmann type reaction with aminopyrimidines derivatives (Scheme 2).

Each compound was fully characterized on the basis of its analytical and spectroscopic properties as IR, ^{1}H and ^{13}C NMR (including DEPT-135) or MS.

As shown in Table 1, this methodology affords the expected products in good to excellent yields.

In all ^{1}H NMR spectra, it is possible to observe the disappearance of the signal between 4.1 and 6.0 ppm due to the proton at the C-5 position from the starting aminopyrimidine. This information together with the appearance of a signal for a quaternary carbon between 111.1 and 113.0 ppm in the ^{13}C NMR spectra, clearly show the thiocyanation of the aminopyrimidine derivatives (signal for isothiocyanates appears at around 130 ppm).[9] These findings are corroborated by FT-IR spectra, which show a signal between 2141 and 2160 cm^{-1} assignable to the thiocyanate group.

On the other hand, the fact that some of the synthesized compounds decompose during melting point measurement (Table 1) could be rationalized on the basis of the different transformations that compounds type **A** can undergo (Scheme 1).[3,11]

We want to comment on two facts in these reactions. The first is that when 2-amino-4,6-dichloropyrimidine was subjected to react under the described conditions, no product was formed. This fact is presumably due to the presence of electron-withdrawing chlorine atoms, which deactivate the pyrimidine ring toward the electrophilic species. The second point concerns 2,4,6-triaminopyrimidine (**7**), which is highly activated, as opposed to 2-amino-4,6-dichloropyrimidine. The reaction takes place in 5 min at 0 °C, and gives a complex mixture of compounds. On the bases of IR and NMR spectra we speculated that that mixture is constituted basically by the thiocyanate derivative **9** (2044 cm^{-1} in the IR spectrum and 111.95 ppm in the ^{13}C NMR) and the corresponding 2-aminothiazolo[4,5-*d*]pyrimidine derivative since in the ^{1}H NMR spectrum there is no signal from 4.0 to 6.0 ppm for the proton at the C-5 position of the starting 2,4,6-triaminopyrimidine.[10]

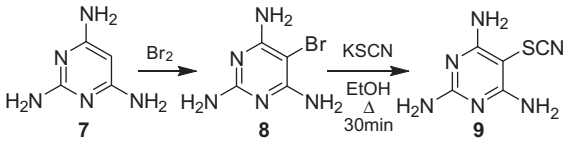
Surprisingly, in the latter case, our findings are in contradiction with those of Baker and Chatfield who claimed the synthesis of compound **9** in refluxing ethanol (Scheme 3).[3]

During the preparation of this manuscript, an article was published that confirms our findings on the reactivity of some triaminopyrimidines toward thiocyanation, and the important role of the 5-thiocyanatopyrimidines that we are reporting here as intermediates in the synthesis of other interesting compounds.[11]

A possible mechanism for the electrophilic thiocyanation of the aminopyrimidine derivatives is depicted in Scheme 4.

Preliminary biological screenings have demonstrated that some of these thiocyanate derivatives exhibit interesting inhibitory action on *Escherichia coli* and *Mycobacterium smegmatatis* cultures.

In conclusion, we have established a new, greener, practical, and efficient methodology which uses molecular iodine for obtain-

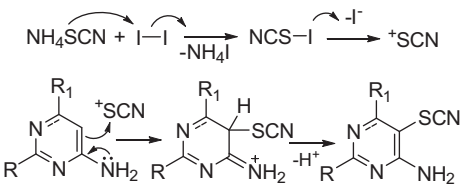


Scheme 3. Reported synthesis of thiocyanate derivative **9**.

Table 1
Products from thiocyanation of aminopyrimidine derivatives: **1a–f**, **3a–f** and **5a**,**b**

Compound[a]	R	R_1	R_2	t^{b} (min)	Yield[c] (%)	Mp[d] (°C)	IR[e] (ν cm^{-1})	^{13}C NMR[f]
2a	SMe	NH_2	NH_2	15	87[g]	197–200	2156	111.2
2b	NH_2	OMe	OMe	20	70	192–194	2155	112.0
2c	SMe	OMe	NH_2	60	75	161–164	2156	111.1
2d	OMe	OMe	NH_2	45	92	155–158	2152	111.4
2e	NH_2	OMe	Me	120	50	190–192	2155	111.6
2f	NH_2	Cl	Cl	____[h]	0	____	____	____
4a	NH_2	H	NH_2	25	90	239–241	2152	113.0
4b	OMe	H	NH_2	20	95	207–210	2155	112.3
4c	SMe	Me	NH_2	20	87	178–181	2156	111.8
4d	SMe	H	NH_2	30	85[i]	208–210	2156	111.2
4e	Me	H	NH_2	30	86	197–199	2141	111.9
4f	OMe	Me	NH_2	35	95	189–193	2156	112.2
6a	—	H	NH_2	70	73[g]	232–234	2160	112.6
6b	—	Me	NH_2	20	86	156–158	2160	112.4

[a] As shown in Scheme 2.
[b] TLC controlled.
[c] Yields of isolated products.
[d] Most of them are actually decomposition rather than melting points.
[e] Absorption band for the thiocyanate group.
[f] Chemical shift for the thiocyano carbon.
[g] Ref. 3.
[h] After 24 h at room temperature.
[i] Ref. 8.



Scheme 4. Proposed mechanism for the thiocyanation.

ing several thiocyanates of aminopyrimidine derivatives, which have been fully characterized, and show promising bioactivities. In addition, these compounds constitute a valuable precursor to potential bioactive fused pyrimidine derivatives bearing a sulfur atom in the heterocyclic nucleus.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.058.

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