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An efficient two-step synthesis of novel 2-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines

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ABSTRACT

A series of novel 2-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines were selectively synthesized by a two-step reaction between 5-amino-3-hetaryl-1*H*-pyrazoles and hetaroyl isothiocyanates with subsequent amination and cyclization promoted by the couple $HgCl_2$/TEA and DMF as solvent. This approach provided the title compounds in good to excellent yields and under mild reaction conditions. The structures of the new compounds were unambiguously established by spectroscopic and analytical techniques.

Introduction

The pyrazolo[1,5-*a*][1,3,5]triazine core can be found in the structure of different biologically active molecules such as antitumoral,[1] antidepressant,[2] anti-inflammatory,[3] and antiviral agents.[4] In particular, 2-amino-derivatives of this system are inhibitors of protein kinase CK2 and cyclin-dependent kinases (CDKs), which exhibit high antiproliferative activity in tumor cell lines and high potential as cancer chemotherapy agents.[1] Recently, it was reported the activity of some 2-aminopyrazolotriazines as corticotropin releasing factor CRF_1 receptor antagonists, hence their potential usefulness for the control and treatment of stress-related diseases such as anxiety and depression.[2e]

The insertion of an amino group into such interesting compounds has usually been accomplished by a reaction of aromatic nucleophilic substitution (S_NAr) between the corresponding 2-chloro-, 2-thiomethyl-, or 2-alkylsulfonylpyrazolotriazine derivatives and the appropriate amine.[1,2e,5] Several steps to prepare the starting pyrazolotriazines are often required, causing an important decrease in the overall yield of the target pyrazolotriazines. Therefore, the development of alternative approaches for efficiently introducing the amino group into the pyrazolotriazine skeleton continues being a significant challenge.

On the other hand, amination of thioureas promoted by the couple mercury(II) chloride and triethylamine ($HgCl_2$/TEA) has been one of the most used reactions to produce guanidines[6] including some examples of cyclic products such as monocyclic triazines,[7] pyridotriazines,[8] and triazino-β-carbolines.[9] However, to the best of our knowledge its use for the synthesis of 2-amino-functionalized pyrazolo[1,5-*a*][1,3,5]triazines has not been reported. Therefore, in connection with our current studies on the synthesis of fused heterocycles containing the pyrazole moiety,[10] we are describing here a two-step reaction between 5-amino-3-hetaryl-1*H*-pyrazoles and hetaroyl isothiocyanates with subsequent amination and cyclization process in the presence of $HgCl_2$/TEA, as an alternative approach to obtain the potentially bioactive 2-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines in good to excellent yields and under mild reaction conditions.

Results and discussion

An efficient two-step sequence to selectively obtain novel 2-aminopyrazolotriazines **5** via the appropriately substituted thiourea derivatives **3** was devised. In the first step, thioureas **3a–d** were prepared according to a procedure recently reported by our group,[10g] by heating a solution of the corresponding hetaroyl isothiocyanates **1a**,**b** and the commercially available 5-aminopyrazoles **2a**,**b** in acetonitrile under reflux for 30 min (Scheme 1). In the second step, pyrazolylthioureas **3a–d** were dissolved in DMF and stirred at room temperature with dimethylamine **4a** or morpholine **4b** for 30 min in the presence of $HgCl_2$/TEA (1:2) equiv to afford the desired 2-aminopyrazolotriazines **5a–h** in excellent yields (Scheme 1, Table 1).[11]

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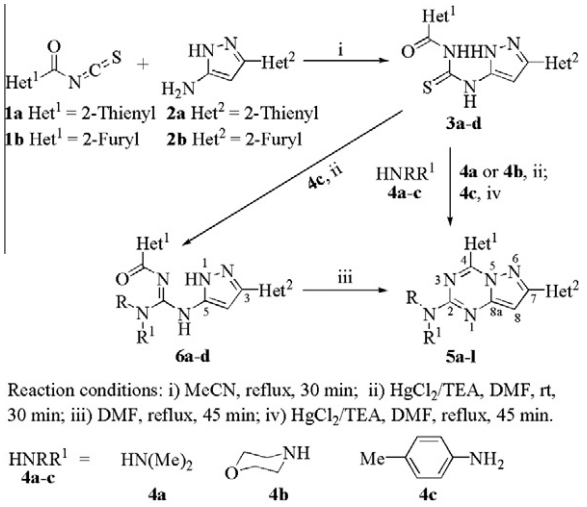


Scheme 1. Synthesis of 2-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines **5** via pyrazolylthioureas **3**.

The reaction of thioureas **3a**–**d** with *p*-toluidine **4c** under the same conditions used for amines **4a**,**b** led to pyrazolylguanidines **6a**–**d**[12] instead of the expected pyrazolotriazines **5i**–**l**. The thermal cyclization of guanidines **6a**–**d** in DMF under reflux afforded the respective pyrazolotriazines **5i**–**l**. It was also found that compounds **5i**–**l** may be directly obtained without the isolation of intermediate guanidines **6a**–**d** by heating the reaction mixture under reflux for 45 min (Scheme 1, Table 1).[11]

In order to expand the scope of the approach described in Scheme 1, pyrazolylthiourea **3a** was reacted with several primary and secondary amines **7a**–**f** (Scheme 2) under the same conditions employed for amines **4a**–**c** in Scheme 1. It was newly found that when secondary amines **7a**,**b** were used, the isolated products corresponded to pyrazolotriazines **8**, **9**. However, when primary amines **7c**–**f** were employed in the process, guanidines **10a**,**b** and **11a**,**b**[12] were formed and they required further heating under reflux to produce the respective pyrazolotriazines **12a**,**b** and **13a**,**b** (Scheme 2, Table 1). Indeed, products **12a**,**b** and **13a**,**b** were directly obtained by heating their starting reaction mixtures under reflux for 60–120 min.[11]

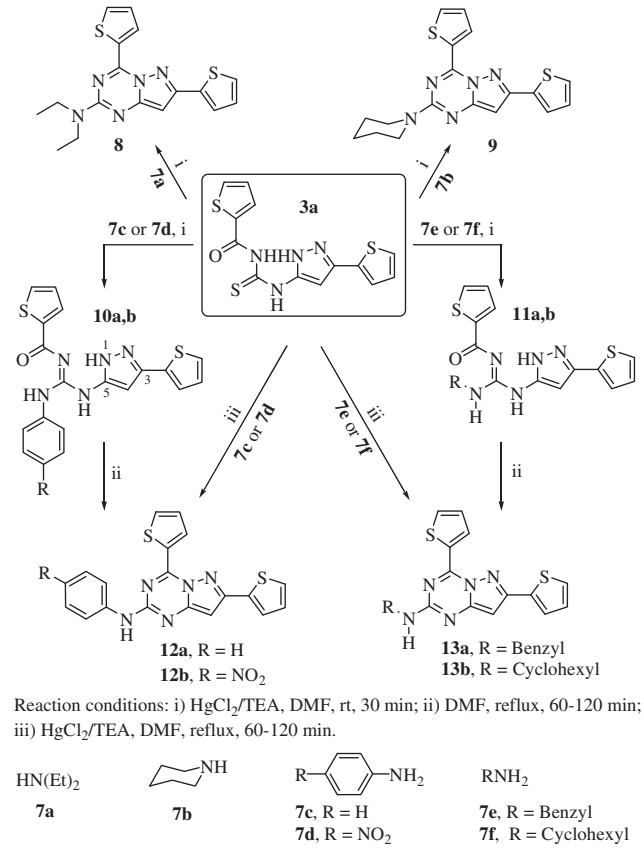
Besides, it was found that the less nucleophilic *p*-nitroaniline **7d** did not react at room temperature with thiourea **3a**, but after heating in DMF under reflux for 120 min, the reaction proceeded and the isolated product corresponded to pyrazolotriazine **12b** in 60% yield (Scheme 2). This fact demonstrated that the reaction is also feasible with amines of low nucleophilicity and that there is a clear influence on both yield and reaction time, depending on the nucleophilic character of the aromatic amine. Accordingly, the reaction with the *p*-nitroaniline **7d** produced a lower yield and required a longer reaction time than their higher nucleophilic analogues *p*-toluidine **4c** (90%, 45 min) and aniline **7c** (71%, 90 min), as shown in Table 1.

The structures of the obtained compounds **5**–**13** were unambiguously established by IR, ^{1}H and ^{13}C NMR spectroscopic techniques, COSY ^{1}H–^{1}H, HSQC, and HMBC experiments, mass spectrometry, and elemental analyses. Spectroscopic data are consistent with the proposed structures **5**–**13**, and the possible formation of the isomeric pyrazolo[3,4-*d*]pyrimidines **14** (Scheme 3), was discarded because the expected absorption bands assignable to the 1-NH stretching were not present in the IR spectra of the isolated cyclic products. This characteristic was easily observed in compounds **5a**–**h**, **8**, and **9**, which contain a secondary amino group as substituent. This finding is also in agreement with their ^{1}H NMR

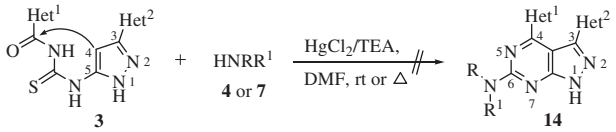
Table 1
Synthesis of 2-amino-substituted pyrazolotriazines **5**, **8**, **9**, **12**, and **13** via pyrazolylthioureas **3**

Product	Het^1	Het^2	NRR^1	Mp (°C)	Yield[a,b] (%)
5a	2-Thienyl	2-Thienyl	Dimethylamino	182	79
5b	2-Furyl	2-Furyl	Dimethylamino	165	81
5c	2-Thienyl	2-Furyl	Dimethylamino	163	76
5d	2-Furyl	2-Thienyl	Dimethylamino	161	82
5e	2-Thienyl	2-Thienyl	Morpholino	164	78
5f	2-Furyl	2-Furyl	Morpholino	211	81
5g	2-Thienyl	2-Furyl	Morpholino	166	85
5h	2-Furyl	2-Thienyl	Morpholino	186	77
5i	2-Thienyl	2-Thienyl	*p*-Toluidino	172	90
5j	2-Furyl	2-Furyl	*p*-Toluidino	200	94
5k	2-Thienyl	2-Furyl	*p*-Toluidino	188	92
5l	2-Furyl	2-Thienyl	*p*-Toluidino	173	91
6a	2-Thienyl	2-Thienyl	*p*-Toluidino	212	92
6b	2-Furyl	2-Furyl	*p*-Toluidino	208	95
6c	2-Thienyl	2-Furyl	*p*-Toluidino	216	93
6d	2-Furyl	2-Thienyl	*p*-Toluidino	222	94
8	2-Thienyl	2-Thienyl	Diethylamino	102	71
9	2-Thienyl	2-Thienyl	Piperidino	124	70
10a	2-Thienyl	2-Thienyl	Anilino	198	89
10b	2-Thienyl	2-Thienyl	*p*-Nitroanilino	[c]	[c]
11a	2-Thienyl	2-Thienyl	Benzylamino	122	88
11b	2-Thienyl	2-Thienyl	Cyclohexylamino	186	92
12a	2-Thienyl	2-Thienyl	Anilino	213	71
12b	2-Thienyl	2-Thienyl	*p*-Nitroanilino	215	60
13a	2-Thienyl	2-Thienyl	Benzylamino	160	80
13b	2-Thienyl	2-Thienyl	Cyclohexylamino	110	83

[a] The yields for products **5i**–**l**, **12a**,**b** and **13a**,**b** correspond to their direct conversion from **3**.
[b] Yields after isolation by column chromatography.
[c] Not isolated.



Scheme 2. Synthesis of 2-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines **8**, **9**, **12**, and **13**.

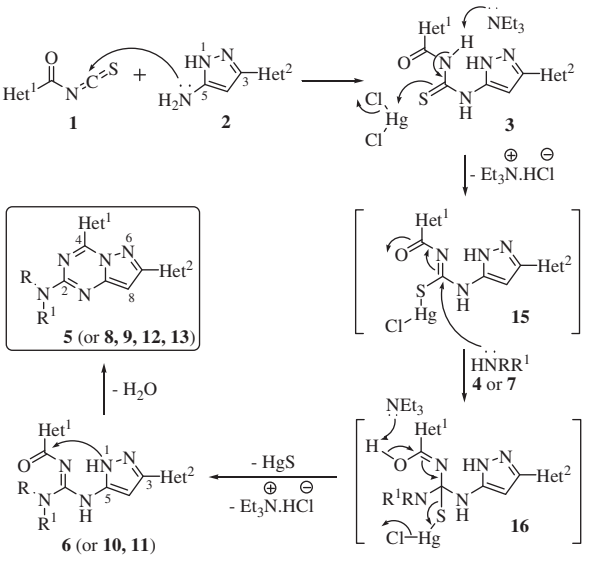


Scheme 3. Discarded isomeric pyrazolo[3,4-*d*]pyrimidines **14**.

spectra, where one of the most representative signals of the products **5**, **8**, **9**, **12**, and **13** corresponded to a singlet between 6.28 and 6.51 ppm assigned to the 8-H proton of their pyrazole moiety, confirming that the structures assigned to the isolated pyrazolotriazines are correct.

A possible mechanistic approach for the selective synthesis of products **5**, **8**, **9**, **12**, and **13** is outlined in Scheme 4. Initially, the N=C=S functionality of the starting materials **1** should suffer a nucleophilic attack from 5-NH_2 of pyrazole **2** leading to the formation of thioureas **3**. Afterward, the $HgCl_2$-promoted guanylation of thioureas **3** with primary and secondary amines **4** or **7** should afford pyrazolylguanidines **6**, **10**, or **11**, presumably, passing through intermediates **15** and **16**. Finally, adducts **6**, **10**, or **11** should be intramolecularly cyclized after the attack of 1-NH of pyrazole moiety over the C=O functionality releasing a molecule of water and generating the isolated pyrazolotriazines **5**, **8**, **9**, **12**, and **13**. Previous reports showing a higher nucleophilicity of 1-NH than the C-4 in intermediates containing a similar pyrazole moiety,[2e,10] support the selective formation of pyrazolotriazines shown in Scheme 4 over their isomeric analogues **14** of Scheme 3.

In order to provide further evidence to support the mechanism depicted in Scheme 4, the following attempts to produce the guanylation and cyclization of the thiourea **3a** with dimethylamine **4a**, were performed. When the experiment was carried out in the absence of the thiophile ($HgCl_2$) and the base (TEA), no reaction was detected after 24 h of stirring at room temperature. However, after $HgCl_2$/TEA (1:2) equiv were added the reaction took place in just 30 min leading to the formation of the expected pyrazolotriazine **5a** in 79% yield. In the other experiment, when the reaction was performed only in the presence of $HgCl_2$, product **5a** was isolated in just 18% yield along with unreacted starting materials. These findings, enabled us to establish that the guanylation/cyclization processes of thioureas **3** through species **15** and **16** (Scheme 4), are efficiently promoted by the couple $HgCl_2$/TEA, which are indispensable for removing the sulfur atom and to trap the two chloride ions, in the form of HgS and $Et_3NH^+Cl^-$, respectively.



Scheme 4. A possible mechanism for the formation of 2-amino-substituted pyrazolotriazines **5**, **8**, **9**, **12**, and **13**.

Conclusions

A practical two-step $HgCl_2$-promoted synthesis of novel 2-amino-substituted pyrazolo[1,5-*a*][1,3,5]triazines displaying good to excellent yields (60–94%) and under mild reaction conditions has been developed. The reaction is applicable to several *N*-hetaroylpyrazolylthioureas and aromatic and aliphatic primary and secondary amines. Various assays demonstrated that pyrazolylthioureas reacted with secondary amines under milder reaction conditions and in shorter reaction times than primary amines. Nevertheless, both primary and secondary amines gave good results for the preparation of the title compounds. The biological interest of the obtained pyrazolotriazines is under investigation and will be reported later.

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11. Procedure for the synthesis of 2-*N*-alkyl, 2-*N*-aryl, and 2-*N*,*N*-dialkylamino-susbstitued pyrazolo[1,5-*a*][1,3,5]triazines **5**, **8**, **9**, **12**, and **13**. *Step 1*: Pyrazolylthioureas **3** were obtained according to the reported procedure.[10g] *Step 2*: $HgCl_2$ (0.02 mol) was added to a solution of the respective pyrazolylthioureas **3a**–**d** (0.02 mol), the corresponding amine **4** or **7** (0.02 mol), and triethylamine (0.04 mol) in DMF (5 mL). The reaction mixture was then stirred at room temperature for 30 min to afford the target pyrazolotriazines **5a**–**h**, **8**, and **9**. Conventional heating of the reaction mixture for 45–120 min was required for the synthesis of pyrazolotriazines **5i**–**l**, **12a**,**b**, and **13a**,**b**. When the reaction finished (TCL control), the crude was diluted with ethyl acetate and filtered through a Celite pad to remove the black precipitate of HgS. Then, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (7:3) as eluent. Data for 4,7-di(2-thienyl)-2-*p*-toluidinopyrazolo[1,5-*a*][1,3,5]triazine (**5i**). For describing the NMR data of compound **5i**, the heteroaromatic rings (Het^1 and Het^2) were denoted with the letters A and B, respectively. Yellow solid; mp 170–172 °C. IR (KBr): *ν* 3425 (NH), 1604, 1516 (C=C, C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.36 (s, 3H, CH_3), 6.51 (s, 1H, H-8), 7.08 (d, *J* = 5.0 Hz, 1H, H_B-5), 7.18 (t, *J* = 2.7 Hz, 1H, H_B-4), 7.23 (d, *J* = 8.7 Hz, 2H, H*o*), 7.24 (s, 1H, exocyclic N–H), 7.32 (t, *J* = 3.8, 1H, H_A-4), 7.60 (d, *J* = 2.7 Hz, 1H, H_B-3), 7.63 (d, *J* = 8.3 Hz, 2H, H*m*), 7.75 (d, *J* = 4.0 Hz, 1H, H_A-5), 8.94 (d, *J* = 3.3 Hz, 1H, H_A-3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.9 (CH_3), 89.7 (C-8), 119.9 (C*o*), 126.7 (C_B-5), 127.0 (C_B-3), 127.8 (C_B-4), 128.5 (C_A-4), 129.5 (C*m*), 132.8 (C_A-2), 132.9 (C_B-2), 134.9 (C_A-5), 136.0 (C*i*), 136.2 (C*p*), 136.8 (C_A-3), 149.0 (C-4), 152.5 (C-8a), 153.6 (C-7), 154.0 (C-2). MS (70 eV) *m*/*z* (%): 389 (100, M^+), 280 (41), 240 (15), 207 (13), 121 (16), 108 (24), 91 (36), 77 (10), 65 (22), 39 (17). Anal. Calcd for $C_{20}H_{15}N_5S_2$: C, 61.67; H, 3.88; N, 17.98. Found: C, 61.73; H, 3.81; N, 17.82.

12. Procedure for the synthesis of 2-*N*-alkyl, 2-*N*-aryl, and 2-*N*,*N*-dialkylamino-substituted 1-hetaroyl-3-(2-hetaryl-1*H*-pyrazol-5-yl)guanidines **6**, **10**, and **11**. The same conditions used to synthesize compounds **5a**–**h**, **8**, and **9** were employed to prepare guanidines **6**, **10**, and **11**. These products were purified by column chromatography on silica gel, using a mixture of hexanes/ethyl acetate (3:2) as eluent. Data for 1-(2-thenoyl)-3-(2-thienyl-1*H*-pyrazol-5-yl)-2-(*N*-p-tolyl)guanidine (**6a**). For describing the NMR data of compound **6a**, the heteroaromatic rings (Het^1 and Het^2) were denoted with the letters A and B, respectively. White solid; mp 210–212 °C. IR (KBr): *ν* 3428, 3250 (NH), 1653 (C=O), 1572, 1474 (C=C, C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): *δ* 2.34 (s, 3H, CH_3), 6.55 (s, 1H, H-4), 7.16 (dd, *J* = 1.8, 3.2 Hz, 1H, H_B-4), 7.19 (t, *J* = 4.3, 1H, H_A-4), 7.27 (d, *J* = 8.3 Hz, 2H, H*o*), 7.54 (d, *J* = 3.3 Hz, 1H, H_B-5), 7.60 (d, *J* = 8.3 Hz, 2H, H*m*), 7.63 (d, *J* = 3.3 Hz, 1H, H_B-3), 7.69 (d, *J* = 4.8 Hz, 1H, H_A-5), 7.75 (d, *J* = 3.8 Hz, 1H, H_A-3), 10.75 (s, 1H, N-H *p*-tolyl), 12.46 (s, 1H, exocyclic N–H), 13.37 (s, 1H, endocyclic N–H),. ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 20.5 (CH_3), 93.2 (C-4), 122.4 (C*m*), 125.6 (C_B-5), 127.0 (C_A-5), 127.9 (C_B-4), 128.2 (C_A-4), 129.2 (C*o*), 130.5 (C*i*), 131.8 (C*p*), 133.6 (C_A-3), 134.8 (C_B-3), 137.8 (C_A-2), 144.1 (C_B-2), 147.8 (C-5), 154.0 (C-3), 163.1 (C-2), 171.4 (C=O). MS (70 eV) *m*/*z* (%): 407 (12, M^+), 389 (97), 280 (44), 240 (11), 207 (100), 193 (17), 147 (18), 133 (15), 121 (12), 108 (16), 91 (39), 73 (54), 65 (11), 44 (57), 39 (17). Anal. Calcd for $C_{20}H_{17}N_5OS_2$: C, 58.95; H, 4.20; N, 17.19. Found: C, 58.67; H, 4.01; N, 17.35.