Tetrahedron Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly selective and efficient synthesis of 3-arylamino-substituted 5-aminopyrazole-4-carboxylates under microwave irradiation

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ARTICLE INFO

Article history:
Received 28 November 2016
Revised 27 December 2016
Accepted 10 January 2017
Available online xxxx

Keywords:
Microwave-assisted synthesis
Selectivity
Pyrazole
Hydrazine

ABSTRACT

An improved microwave-assisted method was developed for the preparation of ethyl 5-aminopyrazole carboxylates from ethyl 2-cyano-3-methylthioacrylates and hydrazine. It was shown that using microwave irradiation significantly reduced the reaction time and improved the process selectivity and yield. The reaction proved to be reproducible in different microwave reactors and on large scale, affording the desired products in high yields and purity. A representative library of 3-arylamino-substituted 5-aminopyrazole-4-carboxylates was successfully prepared to assess the scope of the method.

Molecules constructed using the aminopyrazole skeleton have attracted the significant interest of researchers due to their useful medicinal properties. Aminopyrazoles were reported to possess antiparasitic activity against *Toxoplasma gondii*[1] and *Plasmodium falciparum*.[2] Potentially useful aminopyrazoles for the treatment of lipid disorders, as well as highly potent and selective agonists of the GPR109b receptor were also identified.[3]

The aminopyrazole scaffold was also successfully used for the construction of various therapeutically important kinase inhibitors. Thus, compounds exhibiting potential neuroprotective effects through the inhibition of c-jun N-terminal kinase 3[4] and selectively inhibiting mitogen-activated protein kinase 2,[5] which plays a role in autoimmune diseases, were developed. Recently, aminopyrazoles have been found to possess anticancer activity through inhibition of cyclin-dependent kinase (CDK),[6] p21-activated kinase[7] and Rearranged during Transfection (RET) kinase.[8]

3,5-Diaminopyrazoles have recently been reported as cyclin-dependent kinase 9 (CDK9) inhibitors with the potential to treat multiple myeloma and chronic lymphocytic leukaemia. The diamine CAN508 (**1**)[9] (Fig. 1) represents one of the first CDK inhibitors with high selectivity towards CDK9.[10] Interesting bioactive 3-arylamino-substituted 5-aminopyrazoles have also been identified. Compound **2** demonstrated significant cytotoxicity against the Ehrlich ascites carcinoma cells,[11] while compound **3** was found to possess antibacterial properties.[12]

Aminopyrazoles have been extensively explored as useful building blocks for more complex fused heterocyclic systems, such as pyrazolopyridines, pyrazolopyrimidines, and pyrazolotriazines.[13] Among 5-aminopyrazoles, their 4-cyano derivatives are classical heterocyclic synthons, which have been well-described in the literature and have gained a reputation as useful building blocks for the synthesis of many pyrazole-fused heterocyclic systems.[14] 3-Amino-substituted 5-amino-4-cyanopyrazoles (**6**) have been prepared using the straightforward reaction of 3-amino substituted 3-methylsulfanyl-2-cyanoacrylonitrile (**5**) with hydrazine (Scheme 1).[15] However, replacement of one of the cyano groups of **5** with ethyl carboxylate would give 3-amino-substituted ethyl 2-cyano-3-methylthioacrylates (**8**), which possess both a nitrile and an ester group competing for the nucleophile. Hence, conducting a similar reaction of **8** with hydrazine would result in two possible directions for pyrazole ring closure to give either ethyl 5-aminopyrazole-4-carboxylates (**9**), 3-oxo-2,3-dihydro-1*H*-pyrazole-4-carbonitriles (**10**) or a mixture of these two compounds (Scheme 2).

Reported synthetic procedures based on the reaction of **8** with hydrazine under conventional heating are controversial.[16,17] Initial nucleophilic attack of hydrazine should result in the elimination of methanethiol and subsequent intramolecular cyclization *via* nucleophilic substitution occurs at the ester yielding pyrazole **10**

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http://dx.doi.org/10.1016/j.tetlet.2017.01.028
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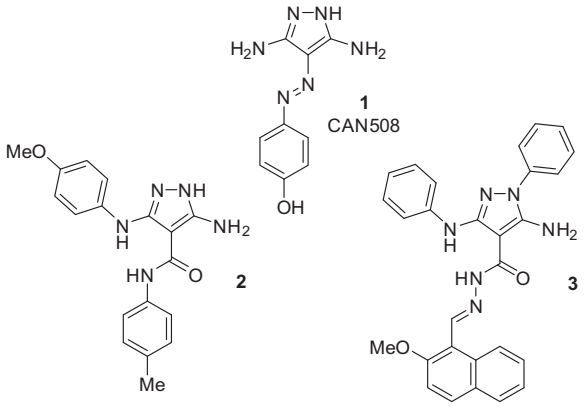


Fig. 1. Selected bioactive 3,5-diaminopyrazoles.

(Pathway B).[16] However, it was also reported that intramolecular cyclization occurred with an alternative nucleophilic attack to the electron deficient carbon of the cyano group affording **9** (Pathway A).[17]

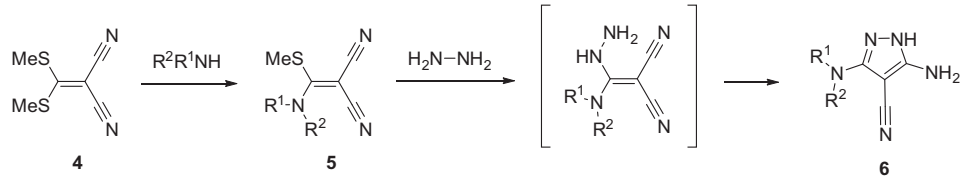
Microwave technology has been demonstrated to speed up reactions, often achieving good purity and product yield.[18] We decided to investigate the selectivity of the reaction between amino-substituted ethyl 2-cyano-3-methylthioacrylates (**8**) and hydrazine and explore the effect of microwave irradiation, which in many cases has been reported to increase the selectivity of chemical reactions.[19]

Following a previously reported method, ethyl 2-cyano-3-methylthio-3-phenylaminoacrylate (**8a**) was prepared from the reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate (**7**) with aniline (Scheme 3).[20] The structure of **8a** was confirmed by NMR spectra, particularly the downfield shifted signal (11.51 ppm in $CDCl_3$) of the NH proton involved in an intramolecular hydrogen bond with the neighbouring ester group. The (*E*)-geometry of **8a** was also supported by 2D NOESY data. The cross peak observed in the 2D NOESY spectrum of **7** between the signals of the ester group and the methylthio groups, was absent in the spectrum of **8a**. Furthermore, single crystal X-ray data for similar compounds[21] suggested the same geometry.

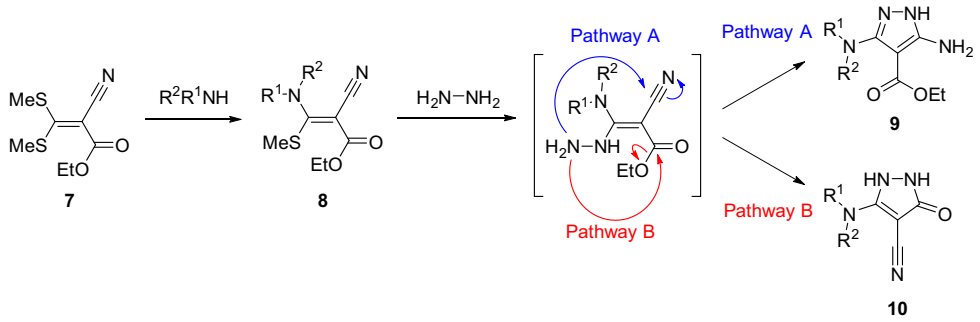
Initially, we attempted the reaction of **8a** with hydrazine using conventional heating at reflux in methanol. Analysis of the crude material showed the presence of a mixture of products, with the major product ethyl 5-amino-3-phenylaminopyrazole-4-carboxylate (**9a**) and minor product 2,3-dihydro-3-oxo-5-phenylaminopyrazole-4-carbonitrile (**10a**) in a 7:3 ratio (Scheme 3). Under these conditions, **9a** was obtained in 53% yield.

An attempt to carry out the reaction of **8a** with hydrazine in methanol under microwave irradiation at 160 °C for 10 min afforded ethyl 5-amino-3-phenylaminopyrazole-4-carboxylate (**9a**) as the major product in high yield (90%). The ring closure showed almost exclusive presence of the desired 5-amino-3-phenylaminopyrazole-4-carboxylate (**9a**) in the crude reaction product; only trace amounts of side-product **10a** were identified by ^{1}H NMR spectroscopy. The desired product **9a** was easily isolated in analytically pure form *via* recrystallization from methanol.

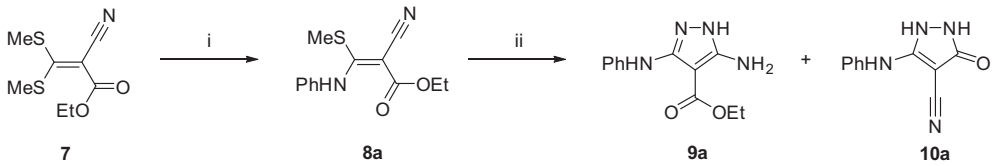
The ester group on the pyrazole ring remained intact as confirmed by the ethoxycarbonyl signals at 1.30 ppm and 4.24 ppm in the ^{1}H NMR spectra. In the ^{13}C NMR spectra, the carbonyl group signal appeared at 164.2 ppm. The deshielding effect of the



Scheme 1. Synthesis of 3-amino substituted 5-amino-4-cyanopyrazoles (**6**).



Scheme 2. Pathways for pyrazole ring closure upon treatment of 3-amino-substituted 2-cyano-3-methylthioacrylates **8** with hydrazine.



Scheme 3. Reagents and conditions: (i) $PhNH_2$ (1 equiv.), MeOH, reflux, 12 h; (ii) N_2H_4 (1 equiv.), MeOH, reflux, 3 h (**9a**, 53% and **10a**, 23%) or N_2H_4 (1 equiv.), MeOH, microwave, 160 °C, 10 min (**9a**, 90% and **10a**, trace).

Please cite this article in press as: Lim F.P.L., et al. Tetrahedron Lett. (2017), http://dx.doi.org/10.1016/j.tetlet.2017.01.028

adjacent ester group resulted in an upfield shifted signal of the pyrazole C-4 at 81.6 ppm. Additionally, the band at 1641 cm^{-1} in the IR spectra corresponding to the carbonyl group, together with no detectable nitrile band, supported the formation of **9a**.

Changing the solvent in the microwave-assisted reaction of **8a** with hydrazine to acetonitrile or tetrahydrofuran had no significant effect on the reaction outcome. The yield and selectivity of the process were similar to those observed for the reaction conducted in methanol.

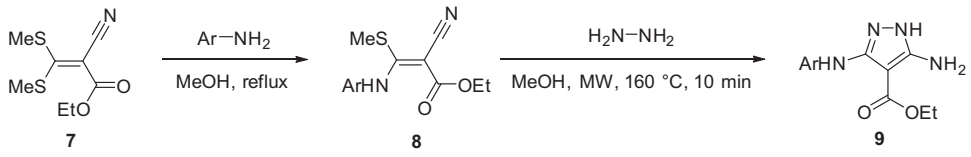
To our satisfaction, increasing the scale of the microwave-assisted reaction to 11.5 mmol under identical microwave irradiation conditions led to the same high purity product and excellent yield (97%).

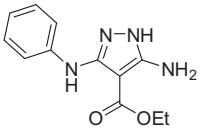
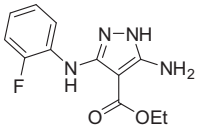
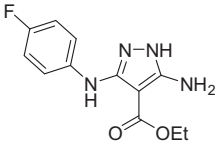
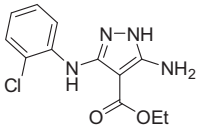
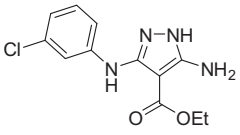
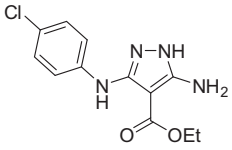
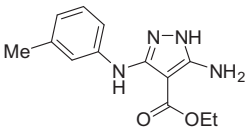
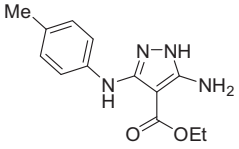
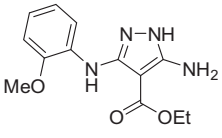
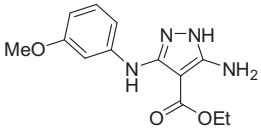
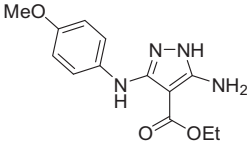
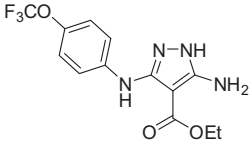
The method was further validated using three different models of microwave synthesizers: Discover SP (CEM), Monowave 450 (Anton Paar), and Initiator+(Biotage). For all three systems, identical temperature settings (160 °C) and reaction time (10 min) were used.

Experiments were performed in triplicate and no significant difference was observed between results obtained using these three instruments. Average yields obtained using Discover SP (CEM), Monowave 450 (Anton Paar), and Initiator + (Biotage) were 90 ± 0.9%, 87 ± 0.5%, and 91 ± 2.8%, respectively.

To test the scope of our newly developed method, a series of 3-arylamino substituted ethyl 2-cyano-3-methylthioacrylates (**8**) was first prepared using the known reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate (**7**) with various anilines.[20] Using our improved protocol, we obtained a library of 3-arylamino-substituted ethyl 5-aminopyrazole-4-carboxylates (**9**) in high yields (up to 99%) and excellent selectivity (Table 1). Only trace amounts of **10** were detected in some of the crude reaction products. It should be noted that the yields obtained with the microwave-assisted method were higher compared to previously reported protocols with a significant decrease in reaction time, requiring just 10 min compared to the reported 3–6 h under conventional heating.[16,17]

Table 1
Synthesis of 3-arylamino-substituted ethyl 5-aminopyrazole-4-carboxylates (**9a-l**).



Product	Structure	Yield (%)[a]	Product	Structure	Yield (%)[a]
9a		90 97[b]	**9g**		91
9b		99	**9h**		90
9c		95	**9i**		83
9d		99	**9j**		87
9e		99	**9k**		70
9f		96	**9l**		99

[a] Yield over two steps; Microwave-assisted step performed on a 1.5 mmol scale in MeOH (4 mL) using a Discover SP CEM microwave synthesizser.
[b] Yield over two steps; Microwave-assisted step performed on a 11.5 mmol scale in MeOH (10 mL) using a Discover SP CEM microwave synthesizer.

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In summary we have successfully developed an improved microwave-assisted method for the synthesis of 3-arylamino-substituted ethyl 5-aminopyrazole-4-carboxylates (**9**). We demonstrated that microwave irradiation significantly shortened the reaction time and substantially improved the reaction selectivity and, as a result, the yield and purity. The scale of the reaction could be increased without adverse effects. The method was also confirmed to be reproducible giving similar results under the same reaction conditions using three different types of microwave reactors. Exploring the reaction scope, we observed a good tolerance to different arylamino substituents allowing the generation of a library of ethyl 5-aminopyrazole-4-carboxylates which may be useful for biological investigation and also as synthons for the construction of more complex molecules and other heterocyclic systems.

Acknowledgements

This work is supported by the Ministry of Higher Education, Malaysia under Fundamental Research Grant Scheme (FRGS) and partially supported by a research grant from Gaia Science (M) Sdn. Bhd. Technical support from Nexus Analytics Sdn. Bhd. and Anton Paar Malaysia Sdn. Bhd. is also appreciated.

A. Supplementary material

These data include experimental details and copies of ^{1}H and ^{13}C NMR spectra of the prepared compounds. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.01.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

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