A novel synthesis of new 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile derivatives

Jabbar Khalafy, Ahmad Poursattar Marjani, Fatemeh Salami

PII: S0040-4039(14)01744-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.10.061
Reference: TETL 45290

To appear in: *Tetrahedron Letters*

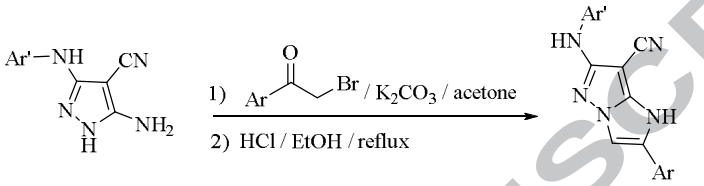
Received Date: 13 August 2014
Revised Date: 1 October 2014
Accepted Date: 9 October 2014

Please cite this article as: Khalafy, J., Marjani, A.P., Salami, F., A novel synthesis of new 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile derivatives, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.10.061

Graphical Abstract

A novel synthesis of new 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile derivatives

Jabbar Khalafy, Ahmad Poursattar Marjani, Fatemeh Salami



Tetrahedron Letters
journal homepage: www.elsevier.com

A novel synthesis of new 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile derivatives

Jabbar Khalafy*, Ahmad Poursattar Marjani, Fatemeh Salami

Departement of Chemistry, Faculty of Science, Urmia University, Urmia 57154, Iran
**Email: jkhalafi@yahoo.com; j.khalafi@urmia.ac.ir*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1*H*-imidazo[1,2-*b*]pyrazole
Cyclocondensation,
5-Amino-1*H*-Pyrazoles
α-Bromoacetophenones

ABSTRACT

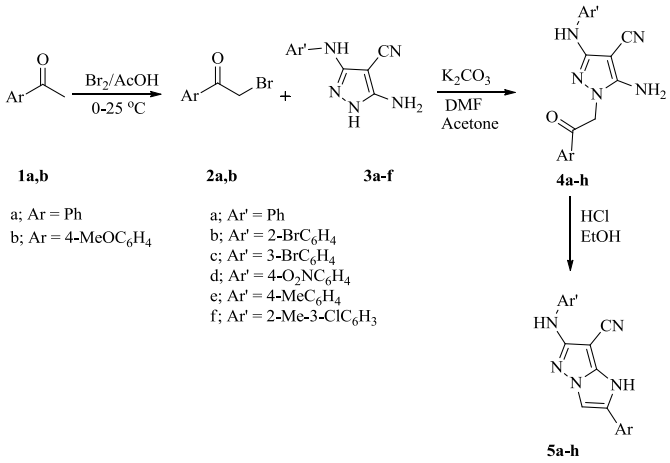
New 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles are synthesized in good yields, via cyclocondensation of 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitriles, which are prepared by the reaction of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitriles and α-bromoacetophenone derivatives in the presence of K_2CO_3 using acetone as the solvent.

The development of new methods for the synthesis of nitrogen-containing heterocycles is very important in organic chemistry. Among various biheterocyclic compounds, bicyclic imidazo[1,2-*b*]pyrazoles exhibit a wide range of biological and pharmaceutical activities such as antitumor,[1-3] herbicidal,[4] anti-inflammatory,[5] antiviral[6] and antineoplastic[7] activities.

Despite there being many literature reports on the synthesis of fused pyrazole derivatives, imidazopyrazoles have rarely been reported. However, there are a variety of methods for the synthesis of imidazo[1,2-*b*]pyrazoles,[8-21] among which, many involve tedious and time-consuming multi-step procedures.

As part of our studies on the synthesis of tri- and tetracyclic heterocycles,[22-25] herein we report a facile method for the synthesis of new derivatives of 1*H*-imidazo[1,2-*b*]pyrazole (**5a-h**) with possible pharmaceutical applications. The synthetic procedure involves the cyclocondensation of 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **4a-h**, which were prepared by the reaction of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitriles **3a-f** and α-bromoacetophenone derivative **2a,b** in the presence of K_2CO_3 using acetone as the solvent.

Bromination of acetophenones **1a,b** in Br_2/AcOH gave the corresponding α-bromoacetophenones **2a,b**.[26] Although the synthesis of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitriles **3a-f** derivaties have been reported,[27] we prepared these by a different method.[28] Reaction of α-bromoacetophenones **2a,b** with pyrazole derivatives **3a-f** gave the corresponding pyrazole intermediates (**4a-h**). Finally, cyclocondensation of compounds **4a-h** by refluxing in ethanol in the presence of hydrochloric acid gave the desired products **5a-h** in 78-93% yields (Scheme 1).



Scheme 1. Synthesis of 2-aryl-6-(arylamino)-1*H*- imidazo[1,2-*b*]pyrazole-7-carbonitiles **5a-h**

Eight examples of the conversion of α-bromoacetophenones **2a,b** into the corresponding substituted 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **4a-h** and 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitiles **5a-h** along with reaction conditions, reaction times, melting points and yields are listed in Tables 1 and 2, respectively.

Table 1. The physical properties and reaction conditions for the synthesis of compounds **4a-h**

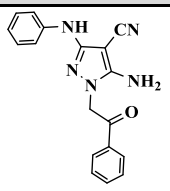
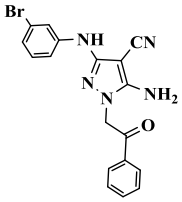
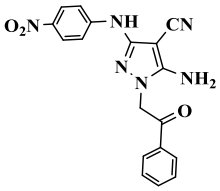
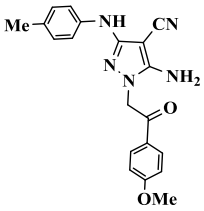
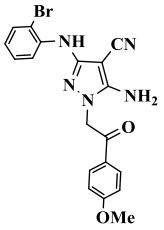
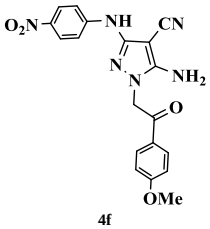
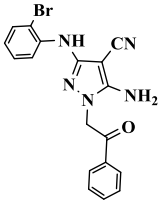
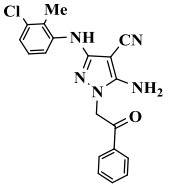
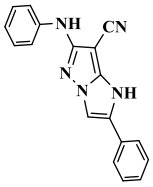
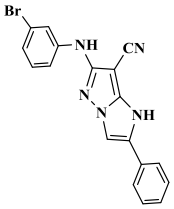
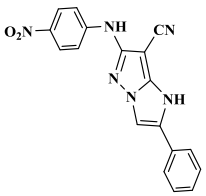
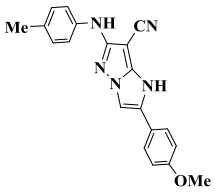
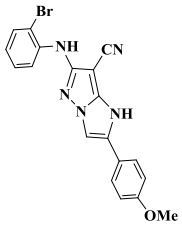
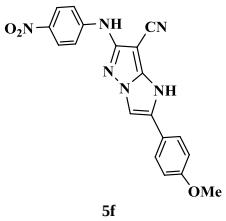
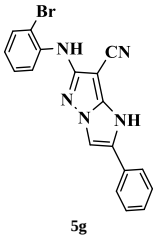
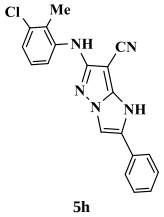
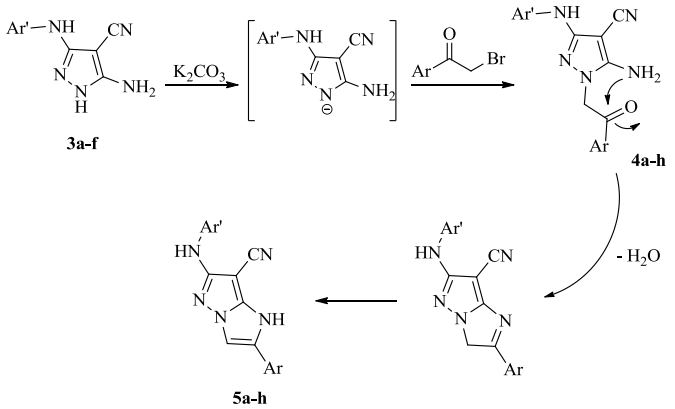
Entry	Intermediate	Temp	Time (h)
1	 **4a**	reflux	1
2	 **4b**	reflux	1
3	 **4c**	r.t	8
4	 **4d**	r.t	10
5	 **4e**	r.t	4
6	 **4f**	r.t	4.5
7	 **4g**	r.t	7
8	 **4h**	reflux	2

Table 2. The physical properties, yields and reaction times for the synthesis of compounds **5a-h**

Entry	Product	Time (h)	Mp (°C)	Yield (%)
1	 **5a**	1.5	265-266 (dec.)	85
2	 **5b**	1	285-286 (dec.)	93
3	 **5c**	1	330 (dec.)	84
4	 **5d**	1	280 (dec.)	78
5	 **5e**	0.5	268-270 (dec.)	90
6	 **5f**	0.75	275 (dec.)	88
7	 **5g**	1	296-298 (dec.)	90
8	 **5h**	2	249	83

The proposed mechanisms for the sequence are shown in Scheme 2. The first step involves the attack of the endocyclic nitrogen atom of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitrile **3a-f,** which is more nucleophilic due to the electron-withdrawing effect of the pyrazole ring, onto α-bromoacetophenone **2a,b** to form intermediates **4a-h**. These are converted into the desired products **5a-h** through intramolecular cyclocondensation of the amino and carbonyl groups.



Scheme 2. The proposed reaction mechanisms for the formation of **4a-h** and **5a-h**.

The structures of all products were confirmed from their ^{1}H NMR, ^{13}C NMR and FT-IR spectral data and by elemental analysis.

In summary, we have described a convenient and facile synthesis of 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles by reaction of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitriles with α-bromoacetophenones in the presence of K_2CO_3, followed by the cyclocondensation of the resulting 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitrile intermediates. The salient features of this procedure are mild reaction conditions, good yields, operational simplicity, ready availability of the starting materials and applications potential for the synthesis of other heterocyclic compounds.

General procedure for the synthesis of 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitriles 4a-h:

5-Amino-1-(2-oxo-2-phenylethyl)-3-(phenylamino)-1*H*-pyrazole-4-carbonitrile (**4a**): A suspension of compound **3a** (199 mg, 1 mmol), α-bromoacetophenone **2** (199 mg, 1 mmol) and K_2CO_3 (140 mg, 1 mmol) in dry acetone (15 mL) and DMF (3 drops) was refluxed for 1 h. The mixture was cooled to room temperature and poured into cold H_2O (30 mL). The precipitate was filtered, washed with cold H_2O (3×5 mL) and dried to give 5-amino-1-(2-oxo-2-phenylethyl)-3-(phenylamino)-1*H*-pyrazole-4-carbonitrile (**4a**) as a yellow solid Mp. 197 ^{o}C.

FT-IR (KBr) (ν_{max}, cm^{-1}): 3426, 3335, 3242, 3058, 2920, 2205, 1691, 1440, 1559, 1494, 1451, 1225, 745, 686, 561. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.44 (1H, s, NH, exchanged by D_2O addition), 8.04 (2H, d, J = 7.2 Hz, arom), 7.73 (2H, t, J = 7.4 Hz, arom), 7.61 (2H, t, J = 7.8 Hz, arom), 7.48 (2H, dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, arom), 7.72 (2H, t, J = 8 Hz, arom), 6.79 (2H, br s, NH_2, exchanged by D_2O addition), 5.50 (2H, s, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 193.26, 153.42, 150.67, 142.85, 134.97, 134.33, 129.31, 128.89, 128.52, 119.70, 116.73, 115.59, 63.82, 54.46. Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07. Found: C, 68.22; H, 4.62; N, 22.21.

Synthesis of derivatives **4b-h:**

The reaction procedure was as described for **4a**, but the reaction time and conditions were as those reported in Table 1. Only the intermediate **4a** was isolated in pure form and its structure was determined by FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The other intermediates were not isolated and the subsequent reactions was carried out following evaporation of the solvent and addition of EtOH to the residue.

General procedure for the synthesis of 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitiles 5a-h:

Synthesis of 2-phenyl-6-(phenylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (5a):

A suspension of 5-amino-1-(2-oxo-2-phenylethyl)-3-(phenylamino)-1*H*-pyrazole-4-carbonitrile (**4a**) (317 mg, 1 mmol) in absolute EtOH (15 mL) and concentrated HCl (4 drops) was refluxed for 1.5 h. The mixture was cooled to room temperature and poured in cold H_2O (30 mL). The pH of solution was adjusted to 7-8 by addition of dilute NaOH and the precipitate was filtered and washed with cold H_2O (3×5 mL) and dried to give the cyclocondensation product **5a** as a white solid, Mp. 265-266 (dec.) ^{o}C.

FT-IR (KBr) (ν_{max}, cm^{-1}): 3235, 3201, 3161, 3072, 2204, 1622, 1555, 1482, 1301, 692. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 12.74 (1H, br s, NH, exchanged by D_2O addition), 8.88 (1H, s, NH, exchanged by D_2O addition), 8.22 (1H, s, arom), 7.74 (2H, d, J = 8 Hz, arom), 7.59 (2H, d, J = 8.4 Hz, arom), 7.46 (2H, t, J = 7.6 Hz, arom), 7.34 (1H, t, J = 7.2 Hz, arom), 7.26 (2H, t, J = 7.6 Hz, arom), 6.84 (1H, t, J = 7.2 Hz, arom). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 156.32, 142.03, 140.70, 130.31, 129.12, 129.08, 128.69, 127.93, 124.24, 120.02, 116.82, 115.29, 106.32, 55.57. Anal. Calcd for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40. Found: C, 72.32; H, 4.21; N, 23.49.

Synthesis of 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitiles 5b-h:

Absolute EtOH and concentrated HCl were added to the the residue **4b-h** and the mixture was refluxed for appropriate amount of time (Table 2). The mixture was left to cold to room temperature. The resulting precipitate was washed with cold H_2O (3×5 mL) and cold MeOH (5 mL) and dried to give the desired products **5b-h**.

Acknowledgments

The authors gratefully acknowledge the financial assistance from Urmia University.

References and notes

1. Kinnamon, K. E.; Engle, R. R.; Poon, B. T.; Ellis, W. Y.; McCall, J. W.; Pzimianski, M. T. *Proc. Soc. Exp. Biol. Med.* **2000**, *224*, 45.
2. Keshi, O.; Bahar, I.; Jernigan, R. L.; Beutler, J. A.; Shoemaker, R. H.; Sausville, E. A. Covell, D. G. *Anti-Cancer Drug. Des.* **2000**, *15*, 79-98.
3. Ennis, H. L.; Möller, L.; Wang, J. J.; Selawry, O. S. *Biochem. Pharmacol*. **1971**, *20*, 2639.
4. Vicentinia, C. B.; Manfrinia, M.; Mazzantia, M.; Scatturina, A.; Romagnolib, C.; Maresc, D. *Arch. Pharm. Pharm Med. Chem*. **1999**, *332*, 337.
5. Dombroski, M. A.; Letavic, M. A.; McClure, K. F. WO 02072576, **2002**.
6. Pelling, J. C.; Shipman, C. *J. Biochem. Pharmacol*. **1976**, *25*, 2377.
7. Matsumoto, M.; Weckbecker, G.; Cory, J. G. *Cancer Commun*. **1990**, *2*, 1.

8. Koga, H.; Hirobe, M.; Okamoto, T. *Chem. Pharm. Bull.* **1974**, *22*, 482.
9. Elguero, J.; Knutsson, L.; Mignonac-Monden, S. *Bull. Chem. Soc. Fr*. **1975,** 255.
10. Ochi, H.; Miyasaka, T.; Kanada, K.; Arakowa, K. *Bull. Chem. Soc. J*. **1976,** *49*, 1980.
11. Elnagdi, M. H.; Hafez, E. A.; El-Fahham, H. A.; Kandeel, E. M. *J. Heterocycl. Chem.* **1980**, *17*, 73.
12. Elgemeie, G. E. H.; Elfahham, H. A.; Ghozlan, S. A. S.; Elnagldi, M. H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1650.
13. Hammouda, H. A.; El-Barbary, A. A.; Sharaf, M. A. F. *J. Heterocycl. Chem.* **1984**, *21*, 945.
14. Terada, A.; Wachi, K.; Miyazawa, H.; Iizuka, Y.; Tabata, K.; Hasegawa, K. European Patent 353,047, **1988**; *Chem. Abstr*., **1991**, 114, 55777.
15. Langer, P.; Wuckelt, J.; Döring, M.; Schreiner, P. R.; Görls, H. *Eur. J. Org. Chem.* **2001**, 2257.
16. Ming, L.; Guilong, Z.; Lirong, W.; Huazheng, Y. *J. Heterocycl. Chem*. **2005**, *42*, 209.
17. Farag, A. M.; Dawood, K. M. *Heteroatom Chem.* **1997**, *8*, 129.
18. Liubchak, K.; Tolmachev, A.; Nazarenko, K. *J. Org. Chem.* **2012**, *77*, 3365.
19. Lee, K. J.; Kim, D. W.; Kim, B. G. *J. Heterocycl. Chem.* **2003**, *40*, 363.
20. Barsy, M. A.; El-Rady, E. A. *J. Heterocycl. Chem*., **2006**, *43*, 523.
21. Rahmati, A.; Kouzehrash, M. A. *Synthesis* **2011**, 2913.
22. Molla Ebrahimlo, A. R.; Khalafy, J.; Prager, R. H. *Aust. J. Chem.* **2009**, *62*, 126.
23. Molla Ebrahimlo, A. R.; Khalafy, J.; Poursattar Marjani, A.; Prager, R. H. *ARKIVOC.* **2009**, *xii*, 17.
24. Poursattar Marjani, A.; Khalafy, J.; Molla Ebrahimlo, A. R. *Synth.Commun.* **2011**, *41*, 2475.
25. Poursattar Marjani, A.; Khalafy, J.; Molla Ebrahimlo, A. R.; Prager, R. H. *Bull. Korean Chem. Soc.* **2011**, *32*, 2183.
26. Langley, W. D. *Org. Synth*. **1941**, *1*, 127.
27. Harunobu, M.; Toshihiro, N.; Hiroaki, S.; Satoko, K.; Hideki, O.; Hiroshi, K. *Chem. Pharm. Bull*. **2007**, *55*, 881.
28. General procedure for the synthesis of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitrile derivatives **3a-f.** Malononitrile (1 mmol) was added to a solution of sodium ethoxide (1 mmol) in EtOH (10 mL) and the reaction mixture was stirred at r.t. for 15 min. An arylisothiocyanate (1 mmol) was added to the reaction mixture and stirring was continued overnight. Iodomethane (1 mmol) was added and the mixture was stirred for 4-6 h. After completion of the reaction (TLC), cold H_2O (10 mL) was added and the precipitate was filtered off, washed with cold H_2O, and dried to give the corresponding methylene malononitrile derivatives. The methylene malononitrile derivatives (1 mmol) were dissolved in absolute EtOH (10 ml) and hydrazine hydrate (80%, 5 mmol) was added at RT. The reaction mixture was stirred at r.t. until the completion of reaction (TLC) using $CHCl_3$/MeOH/MeCN (30:3:1) as eluent. Addition of ice-H_2O (10 mL) and filtration of the precipitate gave the corresponding pyrazole derivatives in 86-95% yield.