Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A one-pot four-component synthesis of *N*-arylidene-2-aryl-imidazo[1,2-*a*]azin-3-amines

Abbas Rahmati *, Ali Moazzam, Zahra Khalesi

Department of Chemistry, University of Isfahan, PO Box 81746-73441, Isfahan, Iran

ARTICLE INFO

Article history:
Received 31 August 2013
Revised 8 February 2014
Accepted 20 March 2014
Available online xxxx

Keywords:
Multi-component reactions
Imidazo[1,2-*a*]pyrazines
Imidazo[1,2-*a*]pyridine

ABSTRACT

N-Arylidene-2-aryl-imidazo[1,2-*a*]azin-3-amines were synthesized via a one-pot, four-component condensation reaction using a 2-aminoazine, toluene-4-sulfonylmethyl isocyanide ($TsCH_2NC$), and two equivalents of readily available aromatic aldehydes. The reaction was performed in diethyl ether as the solvent, with *p*-toluenesulfonic acid (*p*-TSA) as the catalyst at reflux temperature.

Imidazo[1,2-*a*]azines are an important class of fused heterocyclic compounds which demonstrate a wide spectrum of biological activities.[1] Due to these useful properties, the syntheses of these heterocyclic compounds have been studied extensively. The classical synthetic method for the preparation of imidazo[1,2-*a*]azines involves the condensation of α-haloketones with 2-aminoazines.[2] However, this reaction is not suited for the generation a large number of compounds. Multi-component reactions (MCRs) are widely used in synthetic and combinatorial chemistry to generate large libraries of compounds.[3,4] For this reason, MCR approaches have been used for the synthesis of imidazo[1,2-*a*]azines.[5–8] One of well-known methods is the Groebke-Blackburn–Bienayme three-component reaction that was reported in 1998. In this reaction an isocyanide, an aldehyde, and a 2-aminoazine and/or aminoazole are reacted in the presence of an acid catalyst.[8] In this context, *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines have also been produced by means of MCRs.[9–11] Hulme et al. synthesized *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines using a four-component approach employing trimethylsilyl cyanide, two aldehyde molecules, and 2-aminopyridine (route A, Scheme 1).[9] In similar routes, Voskressensky[10] and Adib[11] generated the same products by using 2-hydroxypropanenitrile and imidazoline-2,4,5-trione instead of trimethylsilyl cyanide (routes B and C, Scheme 1). In continuation of this research, we have synthesized *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines and *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyrazin-3-amines via a one-pot, four-component condensation utilizing toluene-4-sulfonylmethyl isocyanide (route D, Scheme 1).

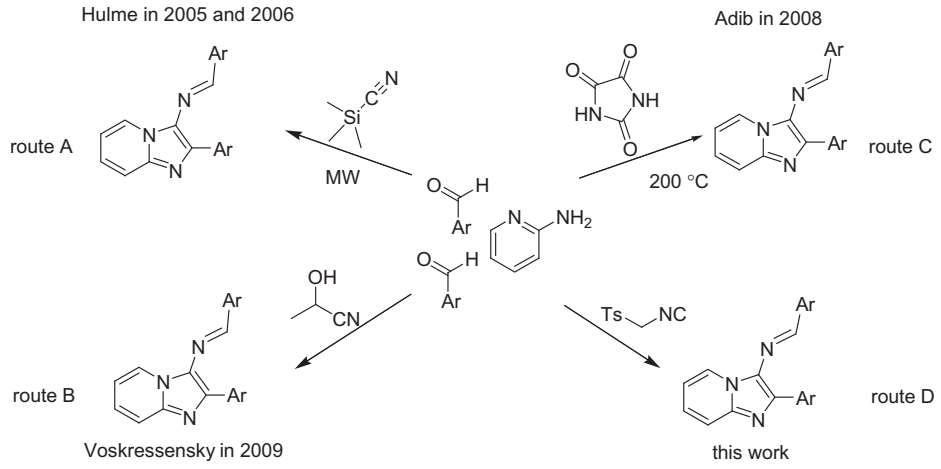
In a pilot experiment, 2-aminopyridine (1 equiv) and *p*-chlorobenzaldehyde (1 equiv) were treated with $TsCH_2NC$ (1 equiv) in acetonitrile (5 mL) in the presence of *p*-toluenesulfonic acid (5 mol %) as catalyst under reflux conditions. After 48 h, monitoring of the reaction showed the presence of a new product along with unreacted starting materials (2-aminopyridine and $TsCH_2NC$). After separation of the reaction mixture, the spectroscopic data of the product indicated that *N*-(4-chlorobenzylidene)-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine (**4a**) had been obtained via a four-component reaction. The results showed that two equivalents of *p*-chlorobenzaldehyde had been incorporated into the structure of the final product (route D, Scheme 1).

To optimize the conditions for this four-component reaction, 2 equiv of *p*-chlorobenzaldehyde with 2-aminopyridine (1 equiv) and $TsCH_2NC$ (1 equiv) was used. First, different solvents in the presence of *p*-TSA (5 mol %), at 15–20 °C and under reflux conditions, were utilized for investigation of the solvent and temperature effects (Table 1). Among the different solvents, diethyl ether was found to be the best solvent (Table 1). Also, between the various temperatures, reflux temperature was the best.

Next, in order to find the best catalyst, a number of Lewis and Bronsted acids (5 mol %) were screened. The employed catalysts are listed in Table 2. The experiments showed that the highest yield was obtained using *p*-TSA as the catalyst. The optimum catalyst loading was next investigated by studying the reaction with different amounts of *p*-TSA under reflux conditions. The best results were obtained in the presence of 5 mol % of *p*-TSA. The results showed that reducing or increasing the amount of catalyst from 5 mol %,

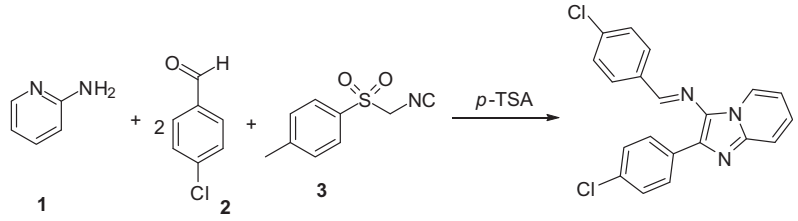
* Corresponding author. Tel.: +98 311 7932730; fax: +98 311 6689732.
E-mail address: a.rahmati@sci.ui.ac.ir (A. Rahmati).

http://dx.doi.org/10.1016/j.tetlet.2014.03.098
0040-4039/



Scheme 1. Methods for the synthesis of *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines.

Table 1
One-pot synthesis of *N*-(4-chlorobenzylidene)-2-(4-chlorophenyl)imidazo [1,2-*a*]pyridin-3-amine in different solvents and at different temperatures[a]



Entry	Solvent	Yield[b] (%)	Yield[b] (%)
1	Et_2O	38[c]	48[d]
2	MeCN	25[c]	37[d]
3	EtOH	20[c]	34[d]
4	MeOH	30[c]	41[d]
5	1,4-Dioxane	0[c]	0[d]
6	DMF	0[c]	22[d]
7	$CHCl_3$	13[c]	20[d]
8	H_2O	0[c]	0[d]
9	[bmim]BF_4	0[c]	12[e]

[a] *p*-Chlorobenzaldehyde (2 mmol), $TsCH_2NC$ (1 mmol), 2-aminopyridine (1 mmol), in the presence of *p*-TSA (5 mol %), solvent (5 mL), 48 h.
[b] Isolated yields.
[c] Reactions run at 15–20 °C.
[d] Reactions run under reflux conditions.
[e] Reaction runs at 100 °C.

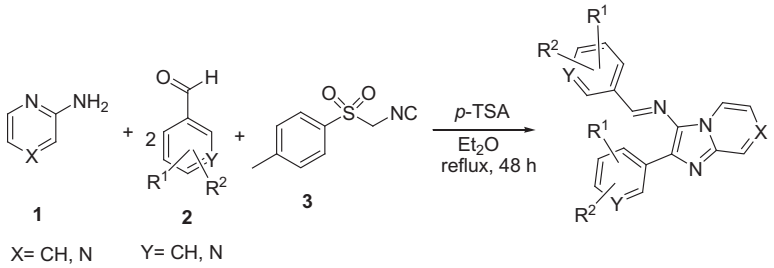
Table 2
Effects of various catalysts on the synthesis of *N*-(4-chlorobenzylidene)-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine[a]

Entry	Catalyst	Amount (%)	Time (h)	Temperature (°C)	Yield[b] (%)
1	Nano-SiO_2-CF_3SO_3H	0.2 g	48	Reflux	30
2	SiO_2-H_2SO_4	0.2 g	48	Reflux	28
3	AcOH	5 mol	48	Reflux	38
4	$InCl_3$	5 mol	48	Reflux	41
5	CF_3SO_3H	5 mol	48	Reflux	14
6	CCl_3CO_2H	5 mol	48	Reflux	11
7	*p*-TsOH	10 mol	48	Reflux	Trace
		7 mol	48	Reflux	36
		5 mol	48	Reflux	48
		2 mol	48	Reflux	34
		1 mol	48	Reflux	23
		0.5 mol	48	Reflux	15
8	*p*-TsOH	5 mol	48	25	42
		5 mol	48	15	38
9	*p*-TsOH	5 mol	6	Reflux	18
		5 mol	12	Reflux	28
		5 mol	24	Reflux	36
		5 mol	72	Reflux	48

[a] Benzaldehyde (2 mmol), $TsCH_2NC$ (1 mmol), 2-aminopyridine (1 mmol), Et_2O (5 mL), reflux.
[b] Isolated yields.

Please cite this article in press as: Rahmati, A.; et al. *Tetrahedron Lett.* (2014), http://dx.doi.org/10.1016/j.tetlet.2014.03.098

Table 3
Synthesis of *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines



Entry	X	Y	R^1	R^2	Product	Yield[a] (%)	Mp (°C)[Ref]
1	CH	CH	4-Cl	H	**4a**	48	163–164
2	CH	CH	4-F	H	**4b**	57	150–151[11a]
3	CH	CH	4-CN	H	**4c**	79	284–286
4	CH	CH	4-NO_2	H	**4d**	82	312–313
5	CH	CH	3-NO_2	H	**4e**	77	289–291
6	CH	CH	2-NO_2	H	**4f**	65	248–250
7	CH	CH	2-Cl	4-Cl	**4g**	69	191–193
8	CH	N	H	H	**4h**	63	223–224[9b]
9	N	CH	3-NO_2	H	**4i**	80	270–272
10	N	CH	2-NO_2	H	**4j**	67	225–226
11	N	CH	2-Cl	4-Cl	**4k**	73	226–228
12	N	CH	2-Cl	6-Cl	**4l**	71	207–209
13	N	CH	2-Cl	6-F	**4m**	67	213–215

[a] Isolated yield.

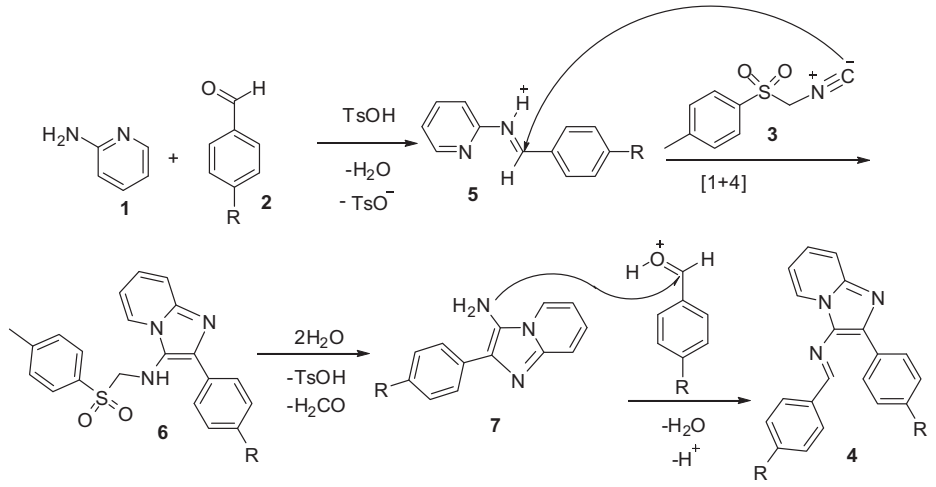
gave decreased yields. The reaction was then repeated at various temperatures (Table 2, entry 8) in Et_2O with the results showing that the best yields were obtained under reflux conditions (Table 2, entries 7 and 8).

To determine the scope and limitations of the reaction, we investigated the use of various substituted benzaldehydes in the presence of 3-aminopyridine or 3-aminopyrazine and toluene-4-sulfonylmethyl isocyanide (Table 3).[12] The reactions proceeded only with aldehydes possessing electron-withdrawing substituents at *ortho*, *meta*, and *para* positions. Benzaldehydes bearing electron-donating substituents did not participate in the reaction under this condition and other conditions attempted.

The structures of products **4a**–**m** were determined from their IR, ^{1}H NMR, ^{13}C NMR, and mass spectra and elemental analyses.[13] All the products are new except for **4b**[11a] and **4h**.[9b]

A mechanistic rationalization for this reaction is provided in Scheme 2. Initially, protonated Schiff base **5** is formed by the addition of the aldehyde to the aminoazine solution in the presence of *p*-toluenesulfonic acid. Next, compound **6** was produced by a non-concerted [4+1] cycloaddition between protonated Schiff base **5** and isocyanide **3**, followed by tautomerization.[8] Subsequently, elimination of *p*-toluenesulfonic acid from **6** and then hydrolysis gives 3-amino-2-aryl-1*H*-imidazo[1,2-*a*]pyridine **7**. Finally, the second equivalent of benzaldehyde reacts with the amine group and generates the *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines **4**.

In conclusion, a convenient and efficient one-pot, four-component synthesis of *N*-arylidene-2-aryl-imidazo[1,2-*a*]pyridin-3-amines is reported from readily available and inexpensive aldehydes, 3-aminopyridine, and tosmic isocyanide starting materials. Also, *N*-arylidene-2-arylimidazo[1,2-a]pyrazin-3-amines are synthesized via this approach. In addition, the proposed method is a new alternative one that could be extended to the synthesis of other types of these compounds. The method also could be considered as a protocol in biochemistry and medicinal discovery.



Scheme 2. A mechanistic rationalization.

Acknowledgement

We gratefully acknowledge financial support from the Research Council of the University of Isfahan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.098.

References and notes

1. (a) Hieke, M.; Rödl, C. B.; Wisniewska, J. M.; la Buscató, E.; Stark, H.; Schubert-Zsilavecz, M.; Steinhilber, D.; Hofmann, B.; Proschak, E. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1969–1975; (b) Hafmann, B.; Franke, L.; Proschak, E.; Tanrikulu, Y.; Schneider, P.; Steinhilber, D.; Schneider, G. *ChemMedChem* **2008**, *3*, 1535–1538; (c) Gueiffier, A.; Mavel, S.; Lhassni, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J. C.; Witvrouw, M.; Balzarini, J.; Clercq, E. D.; Chapat, J. P. *J. Med. Chem.* **1998**, *41*, 5108–5112; (d) Starrett, J. E.; Montzka, T. A.; Crosswell, A. R.; Cavanagh, R. L. *J. Med. Chem.* **1989**, *32*, 2204–2210.
2. (a) Adams, R.; Dix, J. S. *J. Am. Chem. Soc.* **1958**, *80*, 4618–4620; (b) Chichibabin, A. E. *Berichte* **1926**, *59*, 2048–2055.
3. (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005; (b) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969–4009.
4. (a) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: New York, 1998; (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234–6246; (c) Ruijter, E.; Orru, R. V. A. *Drug Discovery Today: Technol.* **2013**, *10*, e15–e20.
5. Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 4487–4490.
6. Veljkovic, I.; Zimmer, R.; Reissig, H.-U.; Brüdgam, I.; Hartl, H. *Synthesis* **2006**, 2677–2684.
7. Adib, M.; Sheikhi, E.; Rezaei, N. *Tetrahedron Lett.* **2011**, *52*, 3191–3194.
8. (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661–664; (b) Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469–5472; (c) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234–2237.
9. (a) Schwerkoske, J.; Masquelin, T.; Perun, T.; Hulme, C. *Tetrahedron Lett.* **2005**, *46*, 8355–8357; (b) Masquelin, T.; Bui, H.; Brickley, B.; Stephenson, G.; Schwerkoske, J.; Hulme, C. *Tetrahedron Lett.* **2006**, *47*, 2989–2991.
10. Polyakov, A. I.; Eryomina, V. A.; Medvedeva, L.; Tihonova, N. I.; Listratova, A. V.; Voskressensky, L. G. *Tetrahedron Lett.* **2009**, *50*, 4389–4393.
11. (a) Adib, M.; Sheibani, E.; Bijanzadeh, H. R.; Zhu, L.-G. *Tetrahedron* **2008**, *64*, 10681–10686; (b) Adib, M.; Sheibani, E.; Zhu, L.-G.; Mirzaei, P. *Tetrahedron Lett.* **2008**, *49*, 5108–5110.
12. *General procedure for the synthesis of N-arylidene-2-aryl-imidazo[1,2-a]pyridin-3-amines* ***4a–m****:* A solution of an aldehyde (0.2 mmol), a 2-aminoazine (0.1 mmol), and *p*-toluenesulfonic acid (0.5 mol%) in Et_2O (5 ml) was magnetically stirred for 12 h at room temperature. Next, $TsCH_2NC$ (0.1 mmol) was added and the mixture was stirred for 36 h at reflux temperature. After completion of the reaction (which was followed by TLC, EtOAc–petroleum ether, 1:5), the solvent was evaporated, and the resulting precipitate was washed with methanol. Finally, pure solid product was obtained by column chromatography.
13. *Characterization data: N*-(4-Chlorobenzylidene)-2-(4-chlorophenyl)imidazo [1,2-*a*]pyridin-3-amine (**4a**): Yellow powder (0.017 g). Yield: 48%. IR (KBr) υ: 3050, 2941, 2548, 1590, 1488, 1463, 1404, 1347, 1230, 1182, 1087, 1010, 929, 825, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.93 (dt, J = 6.8 Hz, J = 1.2 Hz, 1H, H_{arom}), 7.28 (dt, J = 7.4 Hz, J = 1.2 Hz, 1H, H_{arom}), 7.43–7.47 (m, 4H, H_{arom}), 7.60 (d, J = 9.2 Hz, 1H, H_{arom}), 7.79 (dt, J = 8 Hz, J = 0.8 Hz, 4H, H_{arom}), 8.44 (d, J = 6.8 Hz, 1H, H_{arom}), 8.73 (s, 1H, H_{imine}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.7, 117.5, 123.3, 125.6, 129.1, 129.2, 129.5, 129.6, 133.0, 133.3, 133.9, 134.7, 137.5, 143.2, 155.8 ppm. MS (EI, 70 eV): m/z (%): 369 (M^++4, 2), 367 (M^++2, 25), 365 (M^+, 49). Anal. Calcd for $C_{20}H_{13}Cl_2N_3$: C 65.59, H 3.58, N 11.47; Found: C 65.90, H 3.60, N 11.42.