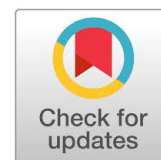




Original Research Article

Saccharin as a new organocatalyzed: a fast, highly efficient and environmentally friendly protocol for synthesis of imidazo[1,2- α]pyridine derivatives *via* a one-three component reaction



Sorour Ramezanzpour^{a,*} , Zahra Bigdeli^a, Frank Rominger^b

^a Department of Chemistry, K. N. Toosi University of Technology, P.O. Box 15875-4416 Tehran, Iran

^b Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

ARTICLE INFORMATION

Received: 7 November 2018
Received in revised: 15 December 2018
Accepted: 16 December 2018
Available online: 10 March 2019

DOI: [10.33945/SAMI/AJGC.2020.1.7](https://doi.org/10.33945/SAMI/AJGC.2020.1.7)

KEYWORDS

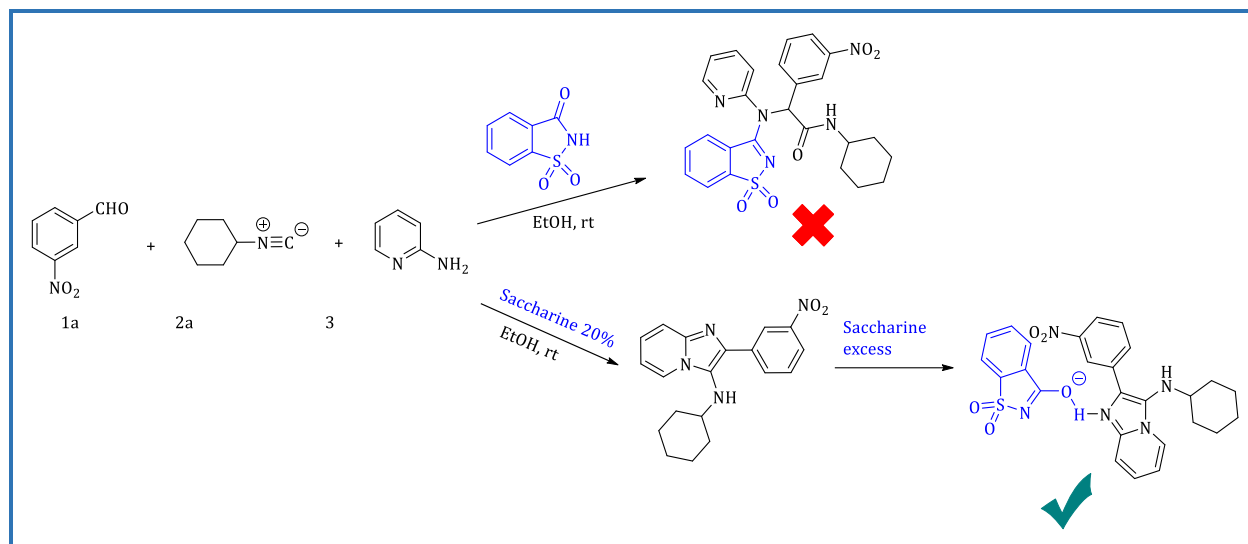
Three-component reaction
Ugi condensation
Saccharin
Imidazo[1,2- α]pyridine

ABSTRACT

In this research article, we report the synthesis of imidazo[1,2- α]pyridine derivatives through Ugi condensation in the presence of saccharin as an organocatalyst used in a three component reaction. The convenient synthetic protocol, short reaction times, easy work up, good to excellent yields and mild reaction conditions make this process both practical and attractive.

© 2020 by SPC (Sami Publishing Company), Asian Journal of Green Chemistry, Reproduction is permitted for noncommercial purposes.

Graphical Abstract



Introduction

Among the most biologically important heterocycle containing *N*-atom, imidazopyridine derivatives are of great concern. That is the imidazole moiety fused with the pyridine ring which shows diverse biological properties due to the probable similar structure with the basic heterocyclic structure of building blocks. Interesting biological activities of imidazopyridine derivatives lead to apply them as antibacterial, antiviral, anti-inflammatory, antitumor, antiviral, antiprotozoal, antipyretic, analgesic, antiapoptotic, hypno selective, agents [1–7]. They have also met new utilities as herbicides and fungicides [8].

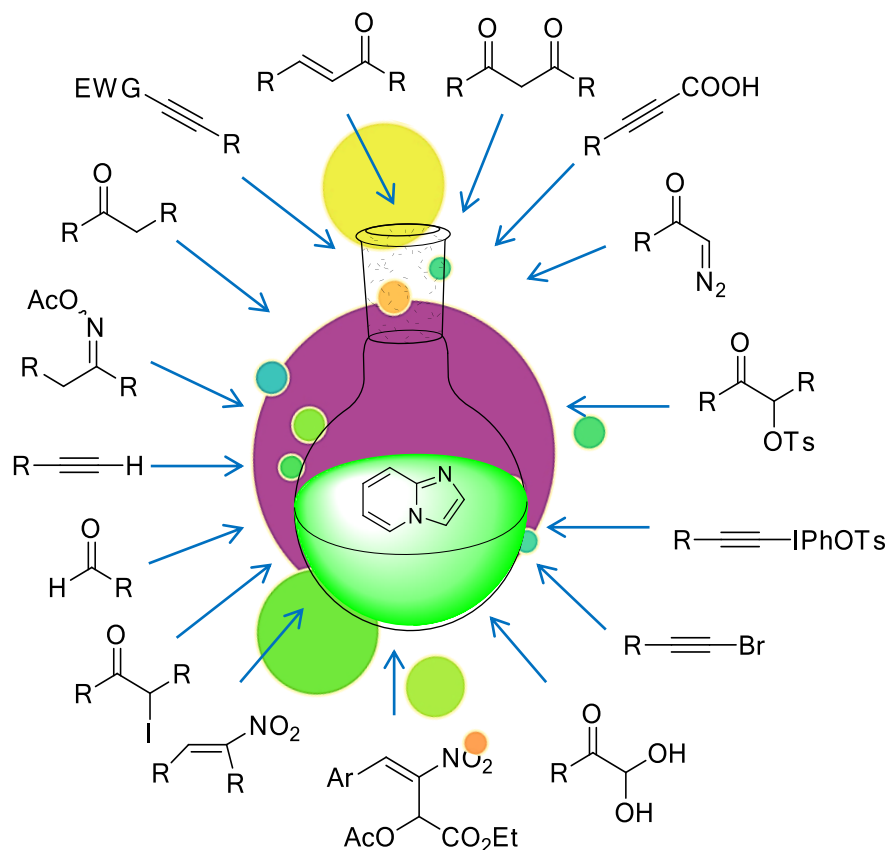
β -amyloid formation inhibitors, GABA and benzodiazepine receptor agonists, and cardiotoxic agents typically contain imidazopyridine moiety [9, 10]. Recently, a new class of imidazopyridine and purine-thioacetamide derivatives has been developed as potent NPP1 inhibitors [11]. There are several drugs containing the imidazo[1,2- α]pyridine moiety such as those used in the treatment of insomnia [12], acute heart failure [13] and peptic ulcer [14]. GSK 812397 and rifaximin also contain this fused heterocyclic moiety that is used for the treatment of infections [15, 16].

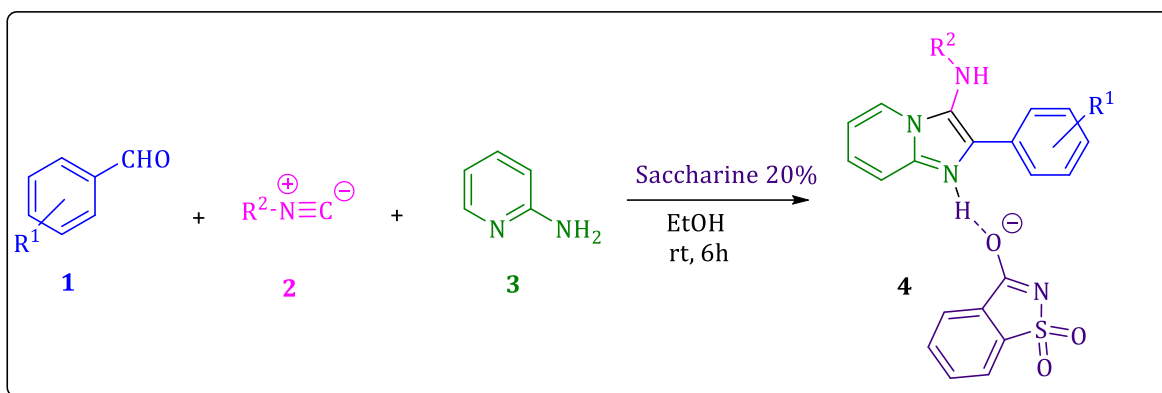
Owing to such chemical and biological interest, a continuous effort is proceeding towards the development of new methods for the synthesis of imidazo[1,2- α]pyridines. Figure 1 shows a schematic illustration of synthetic strategies of imidazo[1,2- α]pyridines presented here into based on the reaction type.

Recently, rapid synthesis of imidazopyridines has been reported by *Li* et al., through C–N coupling mechanism catalyzed by ortho-haloaminopyridines [17]. *Gao* and his coworkers synthesized

imidazopyridine and purine-thioacetamide derivatives as new potential PET tracers for imaging of nucleotide pyrophosphatase/phosphodiesterase (NPP1) [18]. Discovery of a series of imidazopyridine derivatives as novel C-Met kinase inhibitors through established docking studies was investigated by Yang et al., [19]. A novel, efficient, and diastereo selective synthesis of imidazopyridine with high atom economy under microwave activation and [bmIm]OH (1-butyl-3-methylimidazolium hydroxide) promotion from readily available 2-aminopyridine and phenyl acetylene ester has been developed in aqueous condition [20]. An efficient copper-catalyzed aerobic oxidative approach was employed through C–H functionalization of substituted pyridines toward the synthesis of imidazopyridine derivatives in a cascade reaction that involves the cleavage of the N–N bond [21]. In another study, a series of novel radioiodinated imidazopyridine derivatives was synthesized for amyloid- β imaging in alzheimer's disease from bromoketones [22]. Bavetsias et al., [23–26] reported the identification of the novel imidazopyridine derivatives as potent inhibitors of some Aurora kinases which play distinct role in the regulation of mitosis. Rousseau et al., [27] and Adib et al., [28] independently reported the multicomponent synthesis of imidazo[1,2-*a*]pyridines in high yields using 2-aminopyridine, aldehyde and isonitrile. In latter one, the reaction proceeded well in aqueous media without any catalyst.

Figure 1. Imidazo[1,2- α]pyridines from basic starting material





Scheme 1. Synthesis of imidazo[1,2- α]pyridine derivatives through three-component reaction

In recent years, these proteins have been actively pursued as targets for the discovery of new anticancer chemotherapeutics. The first report that clearly shows the cytotoxicity potential of imidazopyridine derivatives to serve as effective molecules against MCF-7 human breast adenocarcinoma cell line was published by Püsküllü et al., [29]. Although a variety of synthetic protocols for imidazopyridine and its derivatives have been reported [30–35] most of them suffer from drawbacks like high temperatures, prolonged reaction times, non-available starting materials, unwanted transition metal catalysts, and poor yields.

A multicomponent reaction (MCRs) is referred to as a unique synthetic reaction in which three or more reactants are involved to form a new product. In such reactions, typically the majority of atoms in the starting materials contribute to the resultant molecule. Multicomponent reactions have been used to develop novel synthetic strategies for the synthesis of different drug-like skeleton and natural products [36]. In our previous work, we designed a four multicomponent reaction to obtain 3-iminosaccharin scaffolds [37] and to achieve our product's different amines. However, when 2-aminopyridine was employed in the reaction we obtained a new product. To identify this new product, NMR, IR, and X-ray were used and all the results confirmed the formation of imidazo[1,2- α]pyridine.

In continuation of our work and to develop a straight forward and efficient protocol, herein we report, for the first time, Ugi three-component condensation of benzaldehydes **1**, cyanides **2** and 2-aminopyridine **3** leading to imidazo[1,2- α]pyridine derivatives **4** organocatalyzed by saccharin. The convenient synthetic protocol, short reaction time, easy work up, good to excellent yields and mild reaction conditions make this work both practical and attractive (Scheme 1). In addition, saccharine was added again at the end of the reaction to obtain the saccharine salt form of the products.

Experimental

Materials and methods

Commercially available materials were used without further purification. Melting points were determined on an electrothermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^1H NMR and ^{13}C NMR spectra were run on Bruker DRX-300 AVANCE, spectrometer at 300 MHz for ^1H NMR, and 75 MHz for ^{13}C NMR. CDCl_3 and $\text{DMSO-}d_6$ were used as solvents. High resolution mass spectra were recorded on HR-MS was recorded on mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer.

General procedure for synthesis of imidazopyridine **4a-h**

To a solution of aldehyde **1** (1 mmol), amine **2** (1 mmol), isocyanide **3** (1 mmol) and saccharine **4** (0.2 mmol) 4 mL EtOH was added. The mixture was stirred for 6 h at ambient temperature. The progress of the reaction was monitored using TLC (*n*-hexane/ethyl acetate, 3:1). After completion of the reaction, the precipitate was filtered and wash with EtOH.

3-(cyclohexylamino)-2-(3-nitrophenyl) imidazo [1,2-*a*] pyridin-1-ium benzo [d] isothiazol-3-olate 1, 1-dioxide (**4a**)

White powder, 363 mg (70%), mp 168–170 °C dec. ^1H NMR (300 MHz, $\text{DMSO-}d_6$): δ 1.02- 1.16 (m, 3H, H Cyclohexyl), 1.24-1.34 (m, 2H, H Cyclohexyl), 1.46-1.50 (m, 1H, H Cyclohexyl), 1.60-1.64 (m, 2H, H Cyclohexyl), 1.76-1.80 (m, 2H, H Cyclohexyl), 2.79-2.90 (m, 1H, -CH, H Cyclohexyl), 5.26 (d, 1H, $J = 15.0$ Hz, NH), 7.20 (t, 1H, $J = 6.4$ Hz, HAr), 7.55 (t, 1H, $J = 6.8$ Hz, HAr), 7.69 (d, 1H, $J = 9.0$ Hz, HAr), 7.75-7.83 (m, 4H, HAr), 7.91 (d, 1H, $J = 6.3$ Hz, HAr), 8.20 (d, 1H, $J = 8.2$ Hz, HAr), 8.57 (t, 2H, $J = 7.4$ Hz, HAr), 9.02-9.04 (m, 1H, HAr). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 24.5, 25.3, 33.5, 56.8, 114, 115, 120.2, 120.9, 122.4, 123.7, 124.5, 127.6, 128.0, 128.6, 130.3, 130.9, 132.4, 133.1, 133.2, 133.4, 139.1, 142.1, 148.2, 164.1. HR-MS (ESI-POS). Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2$ [$\text{M}+1$] $^+$ 337.16642, found 337.16630, Calcd for $\text{C}_{38}\text{H}_{41}\text{N}_8\text{O}_4$ [$2\text{M}+1$] $^+$ 673.32572, found 673.32557, yellow crystal (polyhedron), dimensions 0.150 \times 0.140 \times 0.120 mm³, crystal system triclinic, space group P-1, Z=4, a=9.0763 (8) Å, b=17.1350 (17) Å, c=18.0534 (18) Å, alpha=114.925 (3) deg, beta=94.553 (3) deg, gamma=102.234 (3) deg, V=2442.9 (4) Å³, rho=1.413 g/cm³, T=200 (2) K, Theta_{max}= 21.724 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 5.31 and a completeness of 100.0% to a resolution of 0.96 Å, 30743 reflections measured, 5788 unique (R(int)=0.0850), 3965 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS¹ based on the Laue symmetry of the reciprocal space, mu=0.18 mm⁻¹, T_{min}=0.94, T_{max}=1.00, structure refined against F² with a full-matrix least-squares algorithm using the SHELXL-2014/7 (Sheldrick,

2014) software, 683 parameters refined, hydrogen atoms were treated using appropriate riding models, except those at the nitrogen atoms, which were refined isotropically, goodness of fit 1.04 for observed reflections, final residual values $R1(F)=0.055$, $wR(F^2)=0.121$ for observed reflections, residual electron density -0.50 to 0.24 $e\text{\AA}^{-3}$. CCDC 1571275 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Results and Discussion

We began our investigation using the reaction model between 2-aminopyridine **3**, 3-nitrobenzaldehyde **1a**, cyclohexyl isocyanide **2a** and saccharine. When the model reaction was carried out in ethanol solvent at room temperature, the desired imidazo[1,2-*a*]pyridine product **4a** was obtained in yield 70% (Table 1, entry 1). We proceeded to screen solvent effect, and found that higher product yield was obtained when the reaction was carried in ethanol (69%) (Table 1, entry 1) compared to toluene (10%) and tetrahydrofuran (15%). Further optimization by varying the reaction temperature showed that the model reaction did not occur at room temperature in the absence of saccharine while increasing the reaction temperature to 80 °C completed the reaction due to the catalytic acidity property of saccharine.

Table 1. Optimization of the reaction conditions

Entry	Solvent	Yield of 10a ^a
1	Ethanol	70
2	Methanol	69
3	Toluene	10
4	Tetrahydrofuran	15
5	Dichloromethane	-

^a Isolated yield

Table 2. Optimization of the amount of saccharine in ethanol solvent

Entry	Saccharine (%)	Yield of 10a ^a
1	5	46
2	10	50
3	15	62
4	20	70
5	30	70

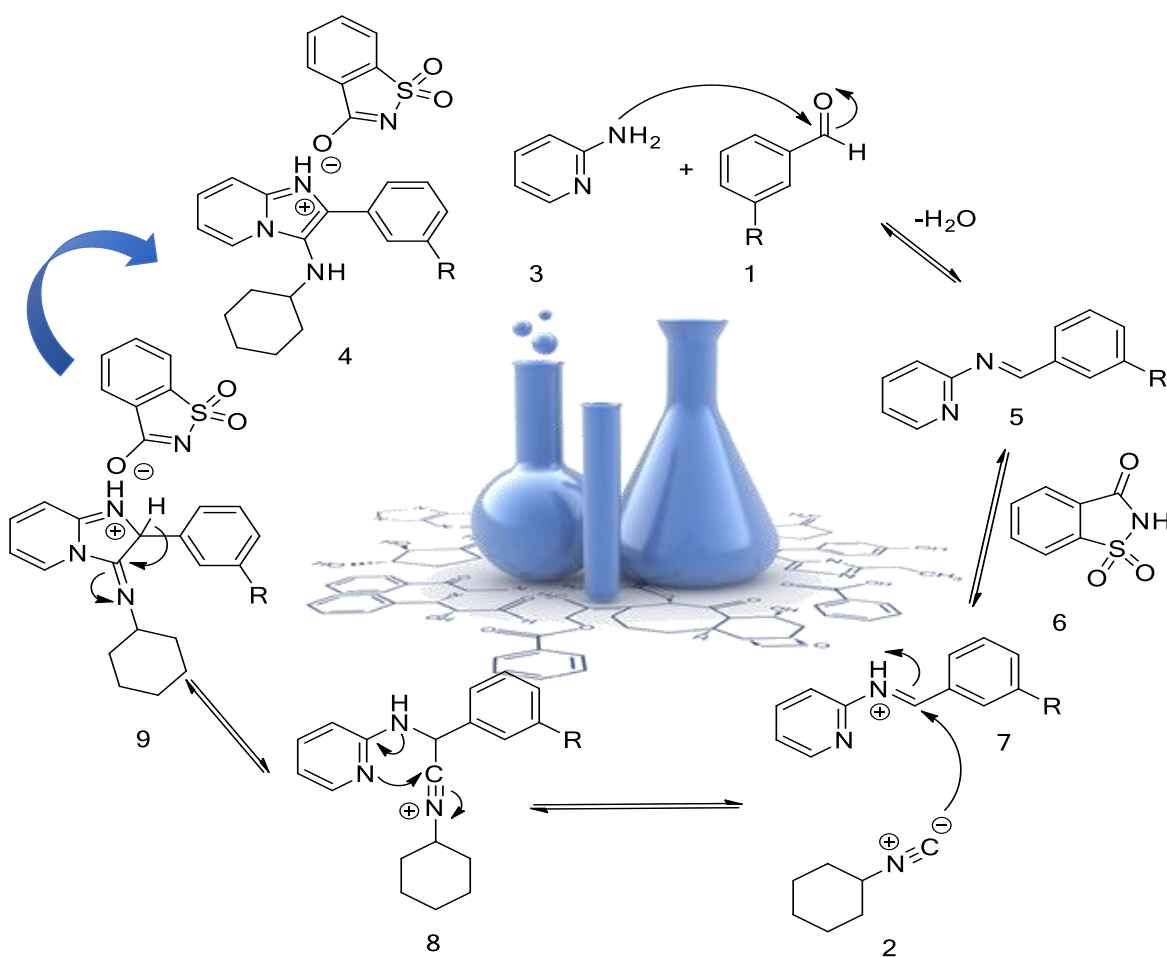
^a Isolated yield

In addition, in order to check out the catalyst's effect on product's yield, we used different amounts of Saccharine (Table 2), 20% catalyst was the best amount to be used (Table 2, entry 4). The ideal condition was achieved when the reaction yield was improved to 70% and the reaction time was reduced to 6 hours.

Based on the experimental results, the probable mechanism path that led to final product is proposed. In the first step, lone pair of the NH_2 group of 2-aminopyridine **3** attacks the electrophilic site of benzaldehyde derivatives **1** under the acid catalyst (Saccharine **6**) resulting the intermediate **7** which then undergoes intramolecular interaction, followed by tautomerism to give imidazopyridine **4** (Scheme 2).

Meanwhile, the result analysis of the X-ray crystallography for compound **4a** is shown in Figure 2 in which intermolecular hydrogen bond is demonstrated.

In Table 3 a library of various skeleton that were synthesized by using different starting material in this reaction are shown.



Scheme 2. The proposed mechanism

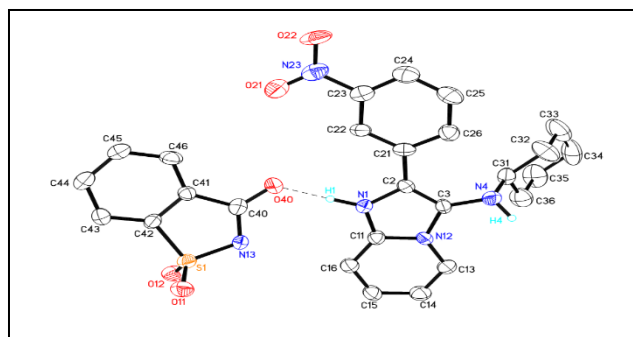
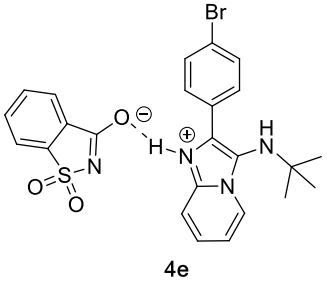
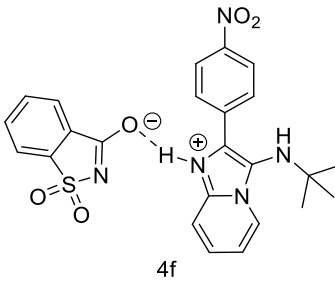
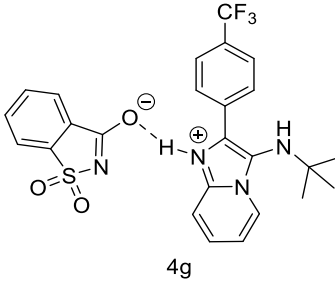
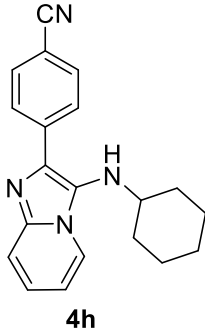


Figure 2. X-ray crystallography for compound **4a**

Table 3.

Entry	Benzaldehyde derivatives	Cyanide derivatives	Product	Yield (%) ^a
1	4-Nitrobenzaldehyde	Cyclohexylisocyanide	<p>4a</p>	70%
2	4-Bromobenzaldehyde	Cyclohexylisocyanide	<p>4b</p>	65%
3	4-Methoxybenzaldehyde	Cyclohexylisocyanide	<p>4c</p>	63%
4	4-Chlorobenzaldehyde	Cyclohexylisocyanide	<p>4d</p>	64%

5	4-Bromobenzaldehyde	<i>tert</i> -Butylisocyanide	 4e	60%
6	4-Nitrobenzaldehyde	<i>tert</i> -Butylisocyanide	 4f	72%
7	4-(Trifluoromethyl)benzaldehyde	<i>tert</i> -Butylisocyanide	 4g	75%
8	4-Cyanobenzaldehyde	Cyclohexylisocyanide	 4h	70%

^a Isolated yield

Acknowledgements

We are thankful to Prof. S. Balalaie for all of his kind guidance, useful discussions, and material support.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Orcid

Sorour Ramezanpour  0000-0002-3901-0391

References

- [1]. Jose G., Kumara T.H.S., Nagendrappa G., Sowmya H.B.V., Jasinski J.P., Millikan S.P., Chandrika N., More S.S., Harish B.G. *Eur. J. Med. Chem.*, 2014, **77**:288
- [2]. Liu C., Chen Q., Yang M., Schneller S.W. *Bioorg. Med. Chem.*, 2013, **21**:359
- [3]. Oslob J.D., Johnson R.J., Cai H., Feng S.Q., Hu L., Kosaka Y., Lai J., Sivaraja M., Tep S., Yang H., Zaharia C.A., Evanchik M.J., McDowell R.S. *ACS Med. Chem. Lett.*, 2013, **4**:113
- [4]. Grädler U., Fuch T., Ulrich W.R., Boer R., Strub A., Hesslinger C., Anézo C., Diederichs K., Zaliani A. *Bioorg. Med. Chem. Lett.*, 2011, **21**:4228
- [5]. Zhu Q., Wanga X., Chu Z., He G., Dong G., Xu Y. *Bioorg. Med. Chem. Lett.*, 2013, **23**:1993
- [6]. Bavetsias V., Faisal A., Crumpler S., Brown N., Kosmopoulou M., Joshi A., Atrash B., Pérez-Fuertes Y., Schmitt J.A., Boxall K.J., Burke R., Sun C., Avery S., Bush K., Henley A., Raynaud F.I., Workman P., Bayliss R., Linardopoulos S., Blagg J. *J. Med. Chem.*, 2013, **56**:9122
- [7]. Kumar Bagdi A., Santra S., Monir K., Hajra A. *Chem. Commun.*, 2015, **51**:1555
- [8]. Moraski G.C., Markley L.D., Chang M., Cho S., Franzblau S.G., Hwang C.H., Boshoff H., Miller M.J. *Bioorg. Med. Chem.*, 2012, **20**:2214
- [9]. Humphries A.C., Gancia E., Gilligan M.T., Goodacre, Hallett D., Marchant K.J., Thomas S.R. *Bioorg. Med. Chem. Lett.*, 2006, **16**:1518
- [10]. Fookes C.J.R., Pham T.Q., Mattner F., Greguric I., Loch C., Liu X., Berghofer P., Shepherd R., Gregoire M.C., Katsifis A. *J. Med. Chem.*, 2008, **51**:3700
- [11]. Chang L., Lee S.Y., Leonczak P., Rozenski J., De Jonghe S., Hanck T., Müller C.E., Herdewijn P. *J. Med. Chem.*, 2014, **57**:10080
- [12]. Langer S.Z., Arbilla S., Benavides J., Scatton B. *Adv. Biochem. Psychopharmacol.*, 1990, **46**:61
- [13]. Mizushige K., Ueda T., Yukiiri K., Suzuki H., *Cardiovasc. Drug Rev.*, 2002, **20**:163
- [14]. Almirante L., Polo L., Mugnaini A., Provinciali E., Rugarli P., Biancotti A., Gamba A., Murmann W. *J. Med. Chem.*, 1965, **8**:305
- [15]. Gudmundsson K., Johns B.A. Imidazo[1,2-a]pyridine derivatives for treatment of herpes viral infections, *United States Patent Application*, 2005, US20060167252
- [16]. Koo H.L., Dupont H.L. *Curr. Opin. Gastroenterol.* 2010, **26**:17
- [17]. Li Ch., Chen L., Steinhuebel D., Goodman A. *Tetrahedron Lett.*, 2016, **57**:2708
- [18]. Gao M., Wang M., Zheng Q.H. *Bioorg. Med. Chem. Lett.*, 2016, **26**:1371
- [19]. Yang Y., Zhang Y., Yang L.Y., Zhao L., Si L., Zhang H., Liu Q., Zhou J. *Bioorg. Chem.*, 2017, **70**:126

- [20]. Waseem M.A., Rahila Ibad A., Ibad F., Neha S., Nazaan J., Saquib M., Siddiqui I.R., *J. Heterocycl. Chem.*, 2017, **54**:1094
- [21]. Yu J., Jin Y., Zhang H., Yang X., Fu H. *Chem. Eur. J.*, 2013, **19**:16804
- [22]. Chen C.J., Bando K., Ashino H., Taguchi K., Shiraishi H., Fujimoto O., Kitamura C., Matsushima S., Fujinaga M., Zhang M.R., Kasahara H., Minamizawa T., Jiang C., Ono M., Higuchi M., Suhara T., Yamada K., Ji B. *Bioorg. Med. Chem.*, 2014, **22**:4189
- [23]. Terao Y., Suzuki H., Yoshikawa M., Yashiro H., Takekawa S., Fujitani Y., Okada K., Inoue Y., Yamamoto Y., Nakagawa H., Yao S., Kawamoto T., Uchikawa O. *Bioorg. Med. Chem. Lett.*, 2012, **22**:7326
- [24]. Newhouse B.J., Wenglowisky S., Grina J., Laird E.R., Voegtli W.C., Ren L., Ahrendt K., Buckmelter A., Gloor S.L., Klopfenstein N., Rudolph J., Wen Z., Li X., Feng B. *Bioorg. Med. Chem. Lett.*, 2013, **23**:5896
- [25]. Wang J., Dyers L., Mason R., Amoyaw P., Bu X.R. *J. Org. Chem.*, 2005, **70**:2353
- [26]. Li G.Y., Jung K.H., Lee H., Son M.K., Seo J., Hong S.W., Jeong Y., Hong S., Hong S.S. *Cancer Lett.*, 2013, **329**:59
- [27]. Rousseau A.L., Matlaba P., Parkinson C.J. *Tetrahedron Lett.*, 2007, **48**:4079
- [28]. Adib M., Mahdavi M., Noghani M.A., Mirzaei P. *Tetrahedron Lett.*, 2007, **48**:7263
- [29]. Püsküllü M.O., Karaaslan C., Bakar F., Göker H. *Chem. Heterocycl. Compd.*, 2015, **51**:723
- [30]. Ramesha A.B., Raghavendra G.M., Nandeesh K.N., Rangappa K.S., Mantelingu K., *Tetrahedron Lett.*, 2013, **54**:95
- [31]. Adib M., Mahdavi M., Abbasi A., Jahromi A.H., Bijanzadeh H.R. *Tetrahedron Lett.*, 2007, **48**:3217
- [32]. Parenty A.D.C., Cronin L. *Synthesis*, 2008, **9**:1479
- [33]. Koubachi J., Berteina-Raboin S., Mouaddib A., Guillaumet G. *Synthesis*, 2009, **2**:271
- [34]. Guchhait S.K., Madaan C. *Org. Biomol. Chem.*, 2010, **8**:3631
- [35]. Shaabani A., Soleimani E., Maleki A., Moghimi J. *Synth. Commun.*, 2008, **38**:1090
- [36]. Zhu J., Bienaymé H., *Multicomponent Reactions*. In Wiley, Weinheim, 2005; p viii
- [37]. Ramezanpour S., Bigdeli Z., Alavijeh N.S., Rominger F. *Synlett.*, 2017, **28**:1214

How to cite this manuscript: Sorour Ramezanpour*, Zahra Bigdeli, Frank Rominger. Saccharin as a new organocatalyzed: a fast, highly efficient and environmentally friendly protocol for synthesis of imidazo[1,2- α]pyridine derivatives via a one-three component reaction. *Asian Journal of Green Chemistry*, 4(1) 2020, 87-97. DOI: [10.33945/SAMI/AJGC.2020.1.7](https://doi.org/10.33945/SAMI/AJGC.2020.1.7)