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Unexpected one pot pseudo four-component reaction for the synthesis of (10*E*)-*N*-benzylidene-2-phenyl*H*-imidazo [1,2-a]pyridin-3-amine derivatives under solvent-free conditions

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Abstract

This work described an efficient pseudo four-component synthesis of (10*E*)-N-benzylidene-2-phenyl*H*-imidazo[1,2-a]pyridin-3-amine derivatives from 2-aminopyridin, malononitrile and arylaldehydes in the presence of NaOH under solvent-free and conventional heating conditions in good to excellent yields. A wide range of aromatic aldehydes would easily undergo condensations with 2-aminopyridin and malononitrile under solvent-free conditions in order to afford the desired products in excellent yields. The use of simple and readily available starting materials, pharmacologically interesting products with applications in bioorganic and medicinal chemistry, and short reaction times are the main advantages of this reaction.

Keywords: Malononitrile; 2-aminopyridin; cyclizations; imidazopyridin; solvent-free.

Introduction

Multicomponent reactions (MCRs) are very powerful methods in organic synthesis. MCRs are those reactions in which more than two simple reactants react in a sequential manner to give complicated products that retain majority of the atoms of the starting material. The main advantages of MCRs include high atom-economy, lower costs, energy saving, shorter reaction times, and complexity of the resulting molecules. MCRs are fast and selective methods for the

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synthesis of large libraries of organic molecules by simply varying each component through a chain of consecutive elementary transformations [1-6].

The imidazo[1,2-a]pyridin derivatives are fused bridgehead nitrogen atom heterocyclic compounds that exhibit a lot of biologically active properties such as anti-secretary and cytoprotective activity (particularly Sch 32651 was mentioned as a promising candidate) [7], proton pump inhibitory (YM-020) [8], partial agonists of the benzodiazepine binding site, exhibiting variable degrees of subtype selectivity, important anxiolytic properties with no evidence of sedation at doses 10-100 times greater than the anxiolytic dose (TP003) [9], the benzodiazepine agonist (Zolpidem) [10], acid-pump antagonist (Sch 28080) [11] and antiviral activity as potent inhibitor of human cytomegalovirus (HCMV) and varicella-zoster virus (VZV) [12] (Figure 1).

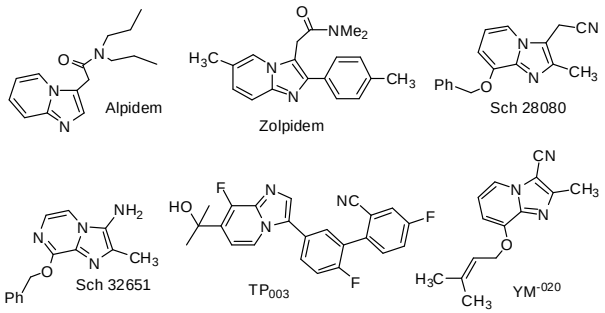
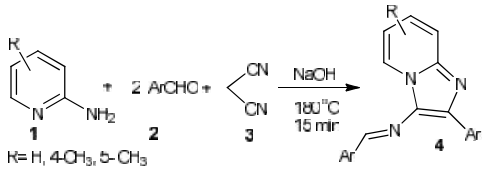


Figure 1. Examples of biologically active imidazo[1,2-a]pyridines, alpidem: agonists of the benzodiazepine binding site; Zolpidem: benzodiazepine agonist; Sch 28080: acid-pump antagonist; TPoo3: anxiolytic property; Sch 32652: anti-secretary and cytoprotective activity; YM-20: Proton pump inhibitory.

The most common synthetic methods reported for the synthesis of imidazo[1,2-a]pyridine heterocyclic systems involve reaction of 2-aminopyridine, benzaldehyde, and imidazoline- 2,4,5-trione under solvent-free and heating conditions [13] or multi-component reaction between an aldehyde, isocyanide and 2-aminopyridine [14-16]. They also have been prepared *via* a multi-step reaction of a vinyl ether, *N*-bromosuccinimide and 2-aminopyridines to afford appropriate imidazo[1,2-a]pyridins [17] or using trimethylsilyl cyanide (TMSCN) or cyanohydrins as the source of cyanide ions in the presence of silica sulfuric acid as catalyst [18]. Some of these methods suffer from three or more sequential synthetic steps, use of expensive or unavailable starting materials and using difficult reaction conditions with low yields of products.

As a part of our efforts on the development of simple methods to prepare biologically active heterocyclic and carbocyclic compounds [19-25], herein we wish to report the synthesis of (10*E*)-*N*-benzylidene-2-phenyl*H*-imidazo[1,2-a]pyridin-3-amine derivatives *via* pseudo

four-component reaction of 2-aminopyridine, malononitrile and arylaldehydes in the presence of NaOH under solvent-free and conventional heating conditions (Scheme 1).



Scheme 1. Synthesis of (10*E*)-*N*-benzylidene-2-phenyl*H*-imidazo [1,2-a]pyridin-3-amines **4a-i**

Experimental

General materials and devices

All starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to monitor the reactions are TLC. Melting points measured on an Electrothermal 9100 apparatus were uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were recorded with a BRUKER DRX-300 AVANCE spectrometer at 300 and 75.5MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded with a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Preparative layer chromatography (PLC) plates were prepared from Merck silica gel (F254) powder.

General procedure for the preparation of 4a-i

The reactions were carried out by mixing the 2-aminopyridin **1** (1 mmol, 0.094 g), malononitrile (1mmol) and arylaldehydes **2** (2 mmol) in the presence of NaOH (0.5 mmol, 0.020 g) under solvent-free conditions stirred at 180 °C in a sealed 5 mL vial in oil bath for 15 minutes. TLC monitoring clearly indicated the formation of corresponding imidazo[1,2-a]pyridine **4**. The product was purified by column chromatography using n-hexane-EtOAc (4:1) as eluent. The solvent was removed and the product was recrystallized from 1:1 n-hexane-EtOAc. The product was obtained as yellow crystals. The ^{1}H and ^{13}C NMR spectroscopes, mass spectrometry and elemental analysis of the product confirmed that formation.

The mp values, elemental analyses, and spectral data of some of these compounds were also in good agreement with those of authentic samples [13].

Characterization data of some of the compounds

(9*E*)-N-(4-chlorobenzylidene)-2-(4-chlorophenyl)*H*-imidazo[1,2-a]pyridin-3-amine (4c, $C_{20}H_{13}N_3Cl_2$)

Yellow crystals; mp 177-178 ^{o}C, yield: 0.66 g, 90%. IR (KBr): 1620, 1422, 1266, 1092, 829 and 771 cm^{-1}. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 6.91 (t, *J* = 6.8 Hz, 1H), 7.43 (m, 5H), 7.60 (d, *J* = 9.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 8.42 (d, *J* = 7.0 Hz, 1H), 8.71(S, 1H). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 116.52, 122.13 (2 CH), 122.59 (C), 26.70, 128.96, 129.23, 129.45, 130.26 and 130.08 (6 CH), 131.39 (C), 131.95 (CH), 134.87 and 137.64, 139.61, 151.18 (4 C), 155.68 (CH). MS: m/z (%) = 365 (89) [M+], 330 (56), 296 (31), 220 (24), 193 (86), 181 (14), 144 (16), 117 (6), 111 (18), 92 (20), 85 (18), 77(100), 69 (17), 57 (22), 51 (13). Anal. Calcd for $C_{20}H_{13}Cl_2N_3$ (366.25): C, 65.58; H, 3.58; N, 11.47. Found: C, 65.72; H, 3.65; N, 11.51%.

(10*E*)-N-((furan-2-yl)methylene)-2-(furan-3-yl)H-imidazo[1,2-a]pyridin-3-amine (4d, $C_{16}H_{11}N_3O_2$)

Yellow crystals; mp 152-154^{o}C, yield: 0.42 g, 75%. IR (KBr): 1634, 1464, 1365, 1265, 1163, 1017 and 701 cm^{-1}. ^{1}H NMR (300.1 MHz, $CDCl_3$) : δ = 6.61 (d.d, ^{3}J = 3.20 Hz, ^{4}J = 1.6 Hz, 1H), 6.64 (d.d, ^{3}J = 3.2 Hz, ^{4}J =1.6 Hz, 1H), 6.91 (t, *J* = 6.8 Hz, 1H), 7.03 - 7.10 (m, 4H), 7.55 (d.d, ^{3}J = 2.0 Hz, 4J = 0.4 Hz, 1H), 7.70 (d.d, ^{3}J = 2.0 Hz, 4J = 0.4 Hz, 1H), 8.47 (d, *J* = 6.80 Hz, 1H), 9.01 (s, CH). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 108.81, 109.54, 109.82, 115.48, 123.12 (5 CH), 124.42 (C), 128.32 (CH), 129.56 (C), 132.88 and 139.24 (2 CH), 140.29 (C), 143.85 and 144.15 (2 CH), 146.43 and 147.35 (2 C), 154.17 (CH). MS: m/z (%) = 278 (23), 277 (45) [M+], 261 (25), 236 (13), 210 (45), 144 (27), 117 (87), 92 (45), 135 (9), 117 (63), 92 (33), 85 (15), 78 (100), 67 (22), 40 (24), 28 (33). Anal. Calcd for $C_{16}H_{11}N_3O_2$ (277.28): C, 69.31; H, 4.00; N, 15.15. Found: C, 69.23; H, 3.91; N, 15.04%.

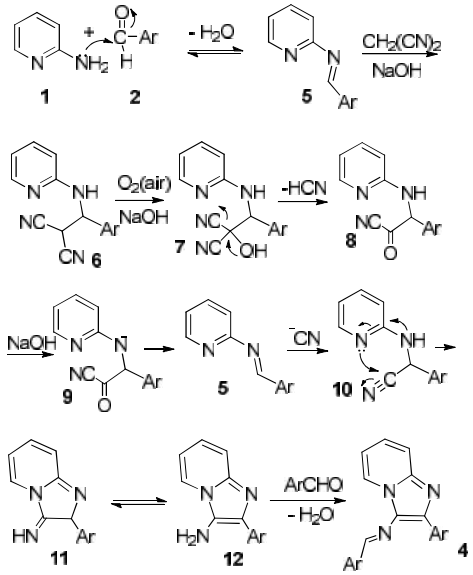
Results and discussion

2-Aminopyridine, malononitrile and arylaldehydes in the presence of NaOH under solvent-free condition produced (10*E*)-N-arylidene-2-aryle*H*-imidazo[1,2-a]pyridin-3-amines **4a-i** in 75-93% yields (Table 1). This reaction was carried out as a pseudo four-component reaction with twice amount of arylaldehydes under heating condition (180 ^{o}C) for 15 minutes.

To optimize this reaction, the first reaction (**4a** preparation) was selected as a model reaction then the effect of NaOH amounts and also other bases such as Et_3N and Na_2CO_3 instead of NaOH and the efficacy of time and temperature to the reaction yields were tested. The results of these experiments displayed in Tables 2 and 3. All of these tests were done in solvent-free condition. Optimum temperature was

examined using the reaction of 2-aminopyridine, malononitrile and benzaldehydes in the presence of the optimum quantity of appropriate base under solvent-free conditions at various temperatures. As can be seen from Tables 2 and 3, the suitable base for this reaction is NaOH and in the composition of 50 mol% of NaOH and 180 ^{o}C the maximum yield was approached (Tables 2 and 3).

Mechanistically, it is reasonable to assume that the first step may involve condensation of 2-aminopyridine **1** and arylaldehyde **2** to form aldimine **5.** Michael addition of a molecule of malononitrile to the aldimine **5** leads to adduct **6.** Oxidization of tertiary C-H in **6** by oxygen in air in the presence of a base provides cyanohydrin **7.** Then, elimination of hydrogen cyanide and formyl cyanide regenerates aldimine **5.** Michael addition by cyanide and then intramolecular cyclization of adduct **10** leads to imine **11.** Condensation of the second molecule of arylaldehyde **2** with intermediate **12** affords product **4** (Scheme 2) [26].



Scheme 2. A plausible mechanism for the formation of the products **4a-i**

Table 1. Synthesis of (10*E*)-*N*-benzylidene-2-phenyl*H*-imidazo [1,2-a]pyridin-3-amines **4a-i**

4	R	Ar	Yield[a]/ %	MP/^{o}C	Lit. Mp/^{o}C[13]
a	H	Ph	88	160-161	161-163
a	H	4-MePh	93	154-155	154-155
c	H	4-ClPh	90	177-178	--
d	H	Furyle	75	152-154	--
e	H	4-OMePh	77	174-175	175
f	H	3-MePh	79	164-166	165
g	H	4-FPh	87	158-159	158-159
h	6-CH_3	4-FPh	78	153-154	154-156
i	7-CH_3	4-OMePh	85	188-190	189-190

[a]Isolated yields

Table 2. Solvent-free synthesis of (10*E*)-*N*-benzylidene-2-phenyl*H*-imidazo [1,2-a]pyridin-3-amine 4a in the presence of Na_2CO_3, Et_3N and NaOH

Entry	Base	Amount of base/mol%	Yield[a]/%
1	Na_2CO_3	10	22
2	Et_3N	10	18
3	NaOH	10	36
4	NaOH	20	55
5	NaOH	30	68
6	NaOH	40	84
7	NaOH	50	95
8	NaOH	60	95
9	No base	0	15

[a]Isolated yields

Table 3. Optimization of conditions for synthesis of (10*E*)-*N*-benzylidene-2-phenyl*H*-imidazo [1,2-*a*]pyridin-3-amine **4a**

Entry	Time	Temperature/^{o}C	Yield[a]/%
1	24 h	25	0
2	5 min	180	41
3	10 min	180	78
4	15 min	180	95
5	20 min	180	95
6	15 min	100	18
7	15 min	140	36
8	15 min	160	65
9	15 min	200	95

[a]Isolated yields

Conclusion

The reported method offers an efficient and simple pseudo four-component synthesis of (10*E*)-N-benzylidene-2-phenyl*H*-imidazo[1,2-a]pyridin-3-amine derivatives from readily available starting materials under solvent-free conditions in good to excellent yields. Short reaction times, preparing pharmacologically interesting product with the applications in bioorganic and medicinal chemistry are the main advantages of this reaction.

Acknowledgments

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