Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-018-1467-z

ORIGINAL PAPER

One-pot sequential double annulations cascade reaction for imidazo[1,2-*b*]pyrazoles synthesis

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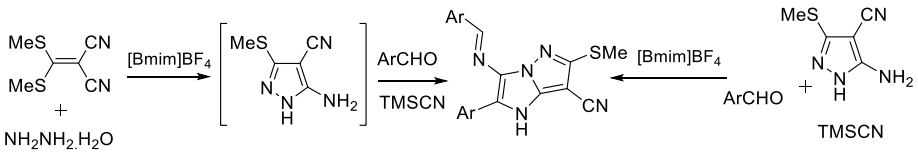
Received: 24 May 2018 / Accepted: 7 August 2018

Abstract
We have developed efficient and green methods for the synthesis of imidazo[1,2-*b*]pyrazole derivatives by Groebke–Blackburn–Bienaymé (GBB) reaction of 5-aminopyrazole, aldehyde and trimethylsilyl cyanid under thermal condition in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [Bmim]BF_4 ionic liquid. A one-pot sequential double annulation cascade reaction has also been demonstrated for imidazo[1,2-*b*]pyrazoles synthesis.

Graphical abstract



Keywords Imidazo[1,2-*b*]pyrazoles · GBB reaction · [Bmim]BF_4 · Sequential reaction · One-pot synthesis

Introduction

One-pot sequential isocyanide-based multi-component reactions, which consist of several simultaneous bond-forming reactions in a one-pot manner, are an attractive and powerful synthetic method for the synthesis of diverse complex molecules from simple precursors [1]. Due to savings in time, chemicals and effort, sequential reactions can increase synthetic efficiency and provide a positive environmental impact by reducing chemical use [1–8]. Among sequential isocyanide-based multi-component reactions, the Groebke–Blackburn–Bienaymé (GBB)-based sequential reactions for heterocycles synthesis are one of the best examples [9–12]. GBB reaction of isocyanides, heterocyclic amidines, and aldehydes via imine formation/ [4 + 1] cycloaddition reaction is an applicable and wide platform for the synthesis of therapeutically-relevant *N*-fused heterocycles [9, 13–16]. Recently, to avoid the use of isocyanide, a new GBB method has been developed using trimethylsilyl cyanide (TMSCN) as a functional isonitrile equivalent [9, 17–23].

Improvement of simple and effective methods for the synthesis of imidazopyrazole frameworks has attracted attention in the area of synthetic and medicinal chemistry because of their outstanding biological activities [24, 25]. They have been reported as anti-inflammatory [26], antifungal [24], and anticancer [27]. Furthermore, some imidazopyrazoles play an important role in the neurodegenerative disorders treatment [28], or the hepatitis C virus [29]. Also, imidazo[1,2-*b*] pyrazole nucleus have been described as photographic dye-forming couplers comprise, useful in photographic materials and processes [30, 31].

There are several methods for the synthesis of imidazo[1,2-*b*]pyrazoles such as intermolecular aza-Wittig reaction of 5-(triphenylphosphoranylideneamino)-3-phenylpyrazole, [32] reaction of 5-amino-pyrazole-4-carbonitriles with α-bromoacetophenones, followed by the cyclocondensation of the resulting intermediates [33], condensation reaction of aldehydes, isocyanide, and

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Published online: 11 August 2018

amino-pyrazole [34, 35], three-steps method from *N*-aryl 2-oxoethanehydrazonoyl bromide [36], and a two-steps method starting from ethyl cyanopyruvate sodium salt and hydrazinoacetaldehyde doethylacetal in the presence of a stoichiometric amount of H_2SO_4 [37]. In spite of potential utility, many of these methods involve expensive reagents in multi-steps manner, strongly acidic conditions, long reaction times and the range of compounds that can be prepared is limited. Therefore, the development of new methods for the preparation of imidazo[1,2-b]pyrazole frameworks is still of much interest. According to the above reports and as a continuation of our interest in synthesis of heterocycles [38, 39], herein, we wish to report synthesis of imidazo[1,2-*b*] pyrazoles by TMSCN-based GBB reaction.

Experimental

Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were taken with a Bomem FT-IR MB spectrometer. The NMR spectra were recorded on a BRUKERDRX-300AVANCE spectrometer. Mass spectra were recorded on an Agilent 5975C VL MSD with Tripe-Axis Detector operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyzer. All chemicals were purchased from Merck or Aldrich and were used without further purification.

General procedure for the synthesis of imidazo[1,2-*b*]pyrazole (6)

A mixture of amino-1H-pyrazole (1 mmol), aldehyde (2 mmol), TMSCN (1.2 mmol) in [Bmim]BF_4 (0.5 g) was heated at 120°C for 24 h. After cooling, the reaction mixture was washed with water (5 mL) and the residue washed with MeOH to afford pure product.

General sequential procedure for the synthesis of imidazo[1,2-*b*]pyrazole (6)

A mixture of 2-(bis(methylthio)methylene)malononitrile (1 mmol) and hydrazine hydrate (1 mmol) in [Bmim] BF_4 (0.5 g) was heated at 70°C for 0.5 h. Then, aldehyde (2 mmol) and TMSCN (1.2 mmol) were added and heated at 120°C for 24 h. After cooling, the reaction mixture was washed with water (5 mL) and the residue washed with MeOH to afford pure product.

The products have low solubility and the ^{13}C NMR data have not been reported.

3-(benzylideneamino)-6-(methylthio)-2-phenyl-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (6a)

Yellow powder. Mp 277–279 °C. IR (KBr) (ν_{max}/cm^{-1}): 3167, 2919, 2222, 1621, 1474. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.70 (3H, s, SCH_3), 7.47–8.14 (10H, m, H-Ar), 9.66 (1H, s, CH), 13.19 (1H, brs, NH). MS (EI): *m*/*z* 357 (M^+, 56), 310 (100), 267 (76), 91 (95). Anal. Calcd for $C_{20}H_{15}N_5S$: C, 67.21; H, 4.23; N, 19.59. Found: C, 67.13 ; H, 4.31; N, 19.47.

3-((4-methylbenzylidene)amino)-6-(methylthio)-2-(p-tolyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (6b)

Yellow powder. Mp 273–275 °C. IR (KBr) (ν_{max}/cm^{-1}): 3244, 3183, 2220, 1619, 1460. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.39 (6H, s, $2CH_3$), 2.68 (3H, s, SCH_3), 7.34–7.39 (4H, m, H-Ar), 7.82 (2H, d, $^3J_{HH}$ = 7.5 Hz, H-Ar), 8.00 (2H, d, $^3J_{HH}$ = 7.5 Hz, H-Ar), 9.60 (1H, s, CH), 13.09 (1H, brs, NH). MS (EI): *m*/*z* 385 (M^+), 357 (100), 106. Anal. Calcd for $C_{22}H_{19}N_5S$: C, 68.55; H, 4.97; N, 18.17. Found: C, 68.68 ; H, 4.88; N, 18.10.

3-((2-bromobenzylidene)amino)-2-(2-bromophenyl)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (6c)

Yellow powder. Mp 289–291 °C. IR (KBr) (ν_{max}/cm^{-1}): 3462, 3156, 2925, 2228, 1617, 1447. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.70 (3H, s, SCH_3), 7.33–7.61 (4H, m, H-Ar), 7.69–7.75 (2H, m, H-Ar), 7.85–7.95 (2H, m, H-Ar), 10.01 (1H, s, CH), 13.36 (1H, brs, NH). MS (EI): *m*/*z* 515 (M^+, 90), 468 (100), 387 (65), 102 (50).

3-((2-chlorobenzylidene)amino)-2-(2-chlorophenyl)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (6d)

Yellow powder. Mp 292–294 °C. IR (KBr) (ν_{max}/cm^{-1}): 3496, 3416, 3145, 2919, 2231, 1620, 1474. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.69 (3H, s, SCH_3), 7.44–7.97 (8H, m, H-Ar), 10.06 (1H, s, CH), 13.36 (1H, s, NH). MS (EI): *m*/*z* 425 (M^+, 50), 378 (100), 240 (74).

3-((4-bromobenzylidene)amino)-2-(4-bromophenyl)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (6e)

Yellow powder. Mp 300–302 °C. IR (KBr) (ν_{max}/cm^{-1}): 3181, 2912, 2220, 1616, 1472. ^1H NMR (300 MHz, DMSO-d_6): δ_H

(ppm) 2.66 (3H, s, SCH_3), 7.67–7.80 (6H, m, H-Ar), 7.94 (2H, d, $^3J_{HH}$ = 6.1 Hz, H-Ar), 9.42 (1H, s, CH), 13.13 (1H, brs, NH). MS (EI): *m/z* 515 (M^+, 25), 512 (45), 487 (100). Anal. Calcd for $C_{20}H_{13}Br_2N_5S$: C, 46.62; H, 2.54; N, 13.59. Found: C, 46.48 ; H, 2.45; N, 13.47.

3-((4-chlorobenzylidene)amino)-2-(4-chlorophenyl)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (6f)

Yellow powder. Mp 301–303 °C. IR (KBr) (ν_{max}/cm^{-1}): 3184, 2221, 1617, 1473. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.66 (3H, s, SCH_3), 7.53–8.03 (8H, m, H-Ar), 9.45 (1H, s, CH), 13.15 (1H, s, NH). MS (EI): *m/z* 425 (M^+, 70), 378 (93), 352 (100).

3-((4-methoxybenzylidene)amino)-2-(4-methoxyphenyl)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (6g)

Yellow powder. Mp 270–272 °C. IR (KBr) (ν_{max}/cm^{-1}): 3416, 3171, 2925, 2826, 2219, 1611, 1514, 1460. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.69 (3H, s, SCH_3), 3.86 (6H, s, $2OCH_3$), 7.13–8.08 (8H, m, H-Ar), 9.57 (1H, s, CH), 12.98 (1H, brs, NH). MS (EI): *m/z* 417 (M^+, 40), 370 (100), 250 (65).

General procedure for the synthesis of pyrazole-imines (7)

A mixture of 5-amino-1H-pyrazole (1 mmol), aldehyde (1 mmol) in [Bmim]BF_4 (0.5 g) was heated at 60°C for 30 min. After cooling, the reaction mixture was washed with water (5 mL) and the residue was washed with $CHCl_3$ to afford pure product **7**.

5-((4-chlorobenzylidene)amino)-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (7a)

Light-yellow powder. Mp 168–170 °C. IR (KBr) (ν_{max}/cm^{-1}): 3284, 3140, 3058, 2921, 2216, 1601, 1549, 1482. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.61 (3H, s, SCH_3), 7.64 (2H, d, $^3J_{HH}$ = 9.0 Hz, H-Ar), 8.01 (2H, d, $^3J_{HH}$ = 9.0 Hz, H-Ar), 9.00 (1H, s, CH), 13.95 (1H, brs, NH). MS (EI): *m/z* 276 (M^+, 100), 243 (30), 150 (50). Anal. Calcd for $C_{12}H_9ClN_4S$: C, 52.08; H, 3.28; N, 20.25. Found: C, 52.15; H, 3.23; N, 20.31.

5-((4-methylbenzylidene)amino)-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (7b)

Light-yellow powder. Mp 165–167 °C. IR (KBr) (ν_{max}/cm^{-1}): 3469, 3135, 2992, 2925, 2214, 1597, 1545, 1489. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 2.46 (3H, s, CH_3), 2.64 (3H, s, SCH_3), 7.32 (2H, d, $^3J_{HH}$ = 7.5 Hz, H-Ar), 7.85 (2H, d, $^3J_{HH}$ = 7.5 Hz, H-Ar), 9.08 (2H, s, CH), 10.48 (1H, brs, NH). MS (EI): *m/z* 256 (M^+, 80), 238 (50), 130 (100).

5-((4-bromobenzylidene)amino)-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (7c)

Light-yellow powder. Mp 174–176 °C. IR (KBr) (ν_{max}/cm^{-1}): 3283, 3131, 3065, 3000, 2927, 2839, 2219, 1609, 1589, 1557, 1483. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.60 (3H, s, SCH_3), 7.77–7.91 (4H, m, H-Ar), 8.97 (1H, s, CH), 13.93 (1H, brs, NH). MS (EI): *m/z* 321 (M^++2, 60), 319 (M^+, 60), 287 (20), 194 (25), 89 (100).

General procedure for the synthesis of imidazo[1,2-*b*]pyrazole (8)

A mixture of pyrazole-imines **7** (1 mmol), aldehyde (1 mmol), TMSCN (1.2 mmol) in [Bmim]BF_4 (0.5 g) was heated at 120°C for 24 h. After cooling, the reaction mixture was washed with water (5 mL) and the residue washed with MeOH to afford pure product **8**.

3-(benzylideneamino)-2-(4-chlorophenyl)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (8a)

Yellow powder. Mp 284–286 °C. IR (KBr) (ν_{max}/cm^{-1}): 3462, 3157, 2922, 2222, 1625 1475. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.68 (3H, s, SCH_3), 7.46–8.11 (9H, m, H-Ar), 9.62 (1H, s, CH), 13.22 (1H, brs, NH). MS (EI): *m/z* 391 (M^+, 50), 344 (90), 91 (100). Anal. Calcd for $C_{20}H_{14}ClN_5S$: C, 61.30; H, 3.60; N, 17.87. Found: C, 61.15; H, 3.52; N, 17.99.

2-(4-chlorophenyl)-3-((4-methoxybenzylidene)amino)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile(8b)

Yellow powder. Mp 287–289 °C. IR (KBr) (ν_{max}/cm^{-1}): 3242, 3159, 2924, 2221, 1622, 1465. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.67 (3H, s, SCH_3), 3.86 (3H, s, OCH_3), 7.06 (2H, d, $^3J_{HH}$ = 8.4 Hz, H-Ar), 7.58 (2H, d, $^3J_{HH}$ = 8.4 Hz, H-Ar), 7.86 (2H, d, $^3J_{HH}$ = 8.4 Hz, H-Ar), 8.08 (2H, d, $^3J_{HH}$ = 8.4 Hz, H-Ar), 9.53 (1H, s, CH), 13.07 (1H, brs, NH). MS (EI): *m/z* 421 (M^+, 90), 348 (60), 287 (100).

3-(benzylideneamino)-6-(methylthio)-2-(p-tolyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (8c)

Yellow powder. Mp 292–294 °C. IR (KBr) (ν_{max}/cm^{-1}): 3236, 3172, 2924, 2222, 1620, 1465. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.38 (3H, s, CH_3), 2.68 (3H, s, SCH_3), 7.35–8.12 (9H, m, H-Ar), 9.61 (1H, brs, CH), 13.07 (1H, brs, NH). MS (EI): *m*/*z* 371 (M$^+$, 95), 324 (100), 91 (85).

3-((4-chlorobenzylidene)amino)-6-(methylthio)-2-(p-tolyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (8d)

Yellow powder. Mp 287–288 °C. IR (KBr) (ν_{max}/cm^{-1}): 3469, 3171, 2925, 2220, 1613, 1473 ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.38 (3H, s, CH_3), 2.67 (3H, s, SCH_3), 7.33–8.07 (8H, m, H-Ar), 9.53 (1H, s, CH), 13.07 (1H, brs, NH). MS (EI): *m*/*z* 405 (M$^+$, 74), 358 (80), 332 (35), 137 (100).

2-(4-bromophenyl)-3-((4-chlorobenzylidene)amino)-6-(methylthio)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (8e)

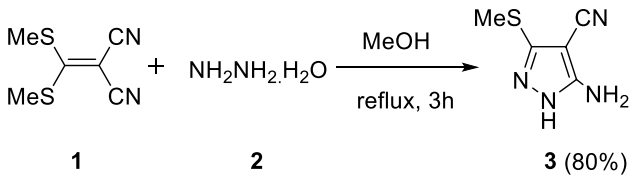
Yellow powder. Mp 295–297 °C. IR (KBr) (ν_{max}/cm^{-1}): 3433, 3178, 2919, 2221, 1618, 1540, 1473. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.67 (3H, s, SCH_3), 7.56–8.04 (8H, m, H-Ar), 9.50 (1H, s, CH), 13.20 (1H, brs, NH). MS (EI): *m*/*z* 471 (M$^+$+2, 60), 469 (M$^+$, 60), 421 (100).

3-((2-chlorobenzylidene)amino)-6-(methylthio)-2-(p-tolyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (8f)

Yellow powder. Mp 275–277 °C. IR (KBr) (ν_{max}/cm^{-1}): 3416, 3173, 2912, 2219, 1614, 1454. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.39 (3H, s, CH_3), 2.70 (3H, s, SCH_3), 7.35–8.01 (8H, m, H-Ar), 9.56 (1H, s, CH), 13.19 (1H, brs, NH). MS (EI): *m*/*z* 405 (M$^+$, 90), 358 (30), 281 (80), 125 (100).

3-((4-methoxybenzylidene)amino)-6-(methylthio)-2-(p-tolyl)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile (8 g)

Yellow powder. Mp 290–292 °C. IR (KBr) (ν_{max}/cm^{-1}): 3235, 3170, 2924, 2220, 1614, 1454. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.37 (3H, s, CH_3), 2.67 (3H, s, SCH_3), 3.84 (3H, s, OCH_3), 7.05–8.06 (8H, m, H-Ar), 9.53 (1H, s, CH), 12.98 (1H, brs, NH). MS (EI): *m*/*z* 401 (M$^+$, 95), 328 (100), 152 (55).



Scheme 1 Synthesis of 5-amino-1*H*-pyrazole **3**

Table 1 Optimization of the reaction conditions

Entry	Solvent	Catalyst	Temperature (°C)	Yield (%)[a]
1	EtOH	–	80	< 10
2	MeOH	–	Reflux	< 10
3	MeCN	–	80	< 10
4	H_2O	–	80	Trace
5	[Bmim]BF_4	–	80	20
6	[Bmim]BF_4	I_2	80	18
7	[Bmim]BF_4	*P*-TSA	80	21
8	[Bmim]BF_4	HCl	80	16
9	[Bmim]BF_4	–	60	Trace
10	[Bmim]BF_4	–	100	46
11	[Bmim]BF_4	–	120	63
12	[Bmim]BF_4	–	140	59
13	–	–	120	37

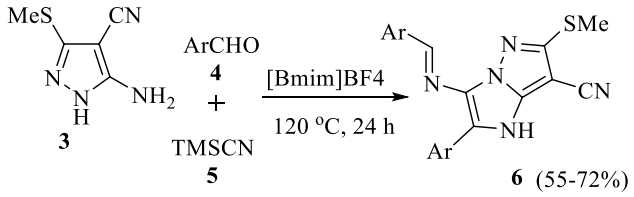
5-amino-1*H*-pyrazole (1 mmol), 4-methylbenzaldehyde (2 mmol), TMSCN (1.2 mmol)

[a]Isolated yields

Results and discussion

First, the 5-amino-1*H*-pyrazole **3** was synthesized by the reaction of 2-(bis(methylthio)methylene)malononitrile **1** and hydrazine hydrate **2** (Scheme 1) [40].

Then, a three-component reaction of 5-amino-1*H*-pyrazole **3**, 4-methylbenzaldehyde **4b** and TMSCN **5** was investigated in different solvents such as EtOH, MeOH, MeCN, H_2O and in [Bmim]BF_4 ionic liquid at 80 °C (Table 1, entries 1–4). The [Bmim]BF_4 ionic liquid was found to be the most suitable reaction media, providing 1*H*-imidazo[1,2-*b*]pyrazole **6b** in 20% yield (Entry 5). When the model reaction was performed in the presence of I_2, *P*-TSA and HCl as catalyst (entry 2), no improvement in the yield was detected (Entries 6–8). To optimize the reaction temperature, we also performed some experiments at 60, 100, 120 and 140 °C (entries 8–12) in [Bmim]BF_4 in the absence of catalyst. As can be seen from Table 1, the most suitable reaction temperature was 120 °C and the desired product **6b** was obtained



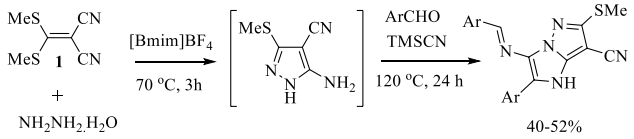
Scheme 2 Synthesis of imidazo[1,2-*b*]pyrazole **6**

Table 2 Synthesis of imidazo[1,2-*b*]pyrazole **6**

Product **6**	Ar	Yield (%)[a]	Yield (%)[b]
a	C_6H_5	58	46
b	4-Me–C_6H_4	63	50
c	2-Br–C_6H_4	64	52
d	2-Cl–C_6H_4	57	43
e	4-Br–C_6H_4	72	51
f	4-Cl–C_6H_4	60	40
g	4-OMe–C_6H_4	55	41

[a]Isolated yields for three-component reaction

[b]Isolated yields for sequential double annulation reaction



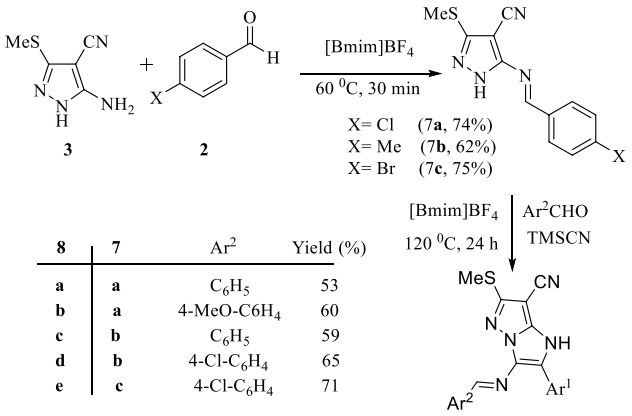
Scheme 3 Sequential synthesis of imidazopyrazole **6**

in 63% isolated yield (entry 10). When this reaction was carried out without [Bmim]BF_4 in neat conditions at 120 °C, the yield of the product was 37% (entry 13).

Then, the scope of the three-component reaction was examined using several substituted aldehydes containing both electron-withdrawing and electron-donating group **4** (Scheme 2 and Table 2) under the optimized reaction conditions and the expected products **6** were obtained in 55–72% isolated yields (Table 2).

After having successfully developed the methodology, a sequential double annulation cascade protocol was examined for the synthesis of imidazo[1,2-*b*]pyrazole **6** directly from 2-(bis(methylthio)methylene)malononitrile **1** and hydrazine hydrate **2** involving nuclephilic substitution/cyclization of **1** and TMSCN-based GBB reaction (Scheme 3). To our delight, the one-pot sequential reaction afforded the desired product **6** in 40–52% isolated yield (Table 2).

The comparison between the yield of three-component reaction ([80 × (55–72)] = 44–57%) with the total yield of sequential double annulation reaction (40–52%) for imidazopyrazole **6** synthesis shows that both methods have almost



8	**7**	Ar^2	Yield (%)
a	**a**	C_6H_5	53
b	**a**	4-MeO-C6H_4	60
c	**b**	C_6H_5	59
d	**b**	4-Cl-C_6H_4	65
e	**c**	4-Cl-C_6H_4	71

Scheme 4 Synthesis of imidazopyrazole **8**

Table 3 Sequential two-step imination/GBB reaction

Product **8**	Solvent	Catalyst	Yield (%)[a]
a	4-Cl–C_6H_4	C_6H_5	40
b	4-Cl–C_6H_4	4-OMe–C_6H_4	54
c	4-Me–C_6H_4	C_6H_5	59
d	4-Me–C_6H_4	4-Cl–C_6H_4	57
e	4-Br–C_6H_4	4-Cl–C_6H_4	64
f	4-Me–C_6H_4	2-Cl–C_6H_4	50
g	4-Me–C_6H_4	4-OMe–C_6H_4	42

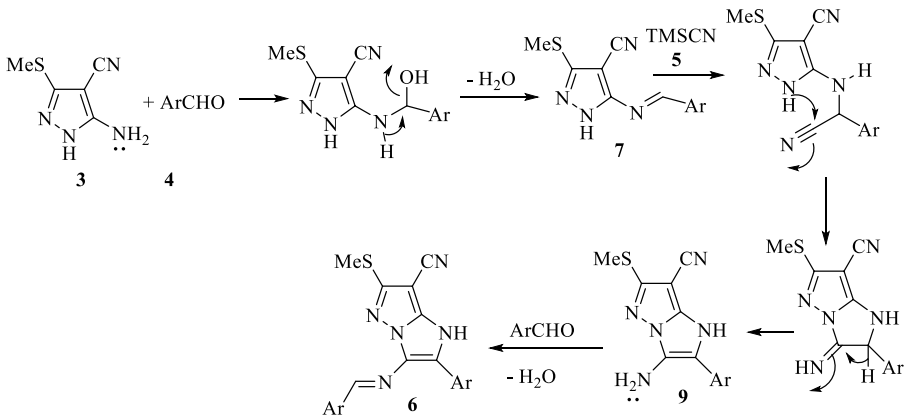
[a]Isolated yields

the same isolated yields. Due to savings in time, solvent and effort, sequential reactions can increase synthetic efficiency and provide a positive environmental impact by reducing chemical use.

During the reaction optimization, it was found, when the reaction of the 5-amino-1H-pyrazole **3**, 4-methylbenzaldehyde **4b** and TMSCN **5** was carried out at 60 °C, the product **6b** was not observed, while 1H-pyrazole-imine **7b** was obtained in 62% isolated yield (Scheme 4). To illustrate the synthetic viability of our methodology, several 1H-pyrazole-imines **7** were synthesized in 62–75% isolated yield at 60 °C after 0.5 h (Scheme 4). The synthesized pyrazole-imines **7** could be a suitable substrate for the synthesis of imidazopyrazole **8** with two different aryl groups. Therefore, the synthetic utility of pyrazole-imines **7** was tested by employing in GBB reaction with aldehydes **4** and TMSCN **5** to provide interesting imidazopyrazole with two different aryl scaffolds **8** in good yields (Scheme 4). This pyrazole-imination reaction and GBB reaction approach can be systematically used for the synthesis of library of imidazopyrazoles **8** in a sequential three-step imination/GBB/imination reaction (Table 3).

The imidazopyrazole **6** apparently results from the formation of pyrazole-imine **7** (formed in situ by reaction of

Scheme 5 Proposed mechanism



5-amino-1*H*-pyrazole **3** and aldehyde **4**). Subsequent nucleophilic reaction of TMSCN **5** and imine **7**, intramolecular cyclization and prototropic shift afforded the intermediate **9**. Finally, the product was produced by the imine formation of intermediate **9** and second molecule of aldehyde **4** (Scheme 5) [9, 17–23, 41, 42].

Conclusions

In this article, new and efficient GBB-based sequential cascade reactions for the synthesis of imidazo[1,2-*b*]pyrazole derivatives are developed from readily available starting materials.

Acknowledgements We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University and the Iran National Science Foundation (INSF) for the financial support of this work.

References

1. S. Sadjadi, M.M. Heravi, N. Nazari, RSC Adv. **6**, 53203 (2016)
2. A. Váradi, T.C. Palmer, R.N. Dardashti, S. Majumdar, Molecules **21**, 19 (2016)
3. A. Dömling, I. Ugi, Angew. Chem. Int. Ed. **40**, 2224 (2001)
4. A. Shaabani, A. Maleki, A.H. Rezayan, A. Sarvary, Mol. Divers. **15**, 41 (2011)
5. Y.M. Yan, Y. Rao, M.W. Ding, J. Org. Chem. **82**, 2772 (2017)
6. M. Krasavin, S. Shkavrov, V. Parchinsky, K. Bukhryakov, Org. Chem. **74**, 2627 (2009)
7. L. Wang, Z.R. Guana, M.W. Ding, Org. Biomol. Chem. **14**, 2413 (2016)
8. S. Balalaie, M. Shamakli, A. Nikbakht, N.S. Alavijeh, F. Rominger, S. Rostamizadeha, H.R. Bijanzadeh, Org. Biomol. Chem. **15**, 5737 (2017)
9. S.K. Guchhait, V. Chaudhary, C. Madaan, Org. Biomol. Chem. **10**, 9271 (2012)
10. G. Martinez-Ariza, M. Ayaz, F. Medda, C. Hulme, J. Org. Chem. **79**, 5153 (2014)
11. T. Kaur, D. Saha, N. Singh, U.P. Singh, A. Sharma, Chem. Select. **3**, 434 (2016)
12. T. Kaur, R.N. Gautam, A. Sharma, Chem. Asian J. **11**, 2938 (2016)
13. S. Shaaban, B.F. Abdel-Wahab, Mol. Divers. **20**, 233 (2016)
14. S.K. Guchhait, C. Madaan, Tetrahedron Lett. **52**, 56 (2011)
15. I. Akritopoulou-Zanze, B.D. Wakefield, A. Gasiecki, D. Kalvin, E.F. Johnson, P. Kovar, S.W. Djuric, Bioorg. Med. Chem. Lett. **21**, 1480 (2011)
16. A.T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S.K. Guchhait, C.N. Kundu, U.C. Banerjee, P.V. Bharatam, J. Med. Chem. **54**, 5013 (2011)
17. J. Schwerkoske, T. Masquelin, T. Perun, C. Hulme, Tetrahedron Lett. **46**, 8355 (2005)
18. T. Masquelin, H. Bui, B. Brickley, G. Stephenson, J. Schwerkoske, C. Hulme, Tetrahedron Lett. **47**, 2989 (2006)
19. E. Bell, A.Y. Shaw, F. De Moliner, C. Hulme, Tetrahedron **70**, 54 (2014)
20. A.I. Polyakov, V.A. Eryomina, L.A. Medvedeva, N.I. Tihonova, A.V. Listratova, L.G. Voskressensky, Tetrahedron Lett. **50**, 4389 (2009)
21. A. Shaabani, A. Maleki, Monatsh. Chem. **138**, 51 (2007)
22. F. Chen, M. Lei, L. Hu, Tetrahedron **69**, 2954 (2013)
23. M. Abdollahi-Alibeik, A. Rezaeipoor-Anari, Catal. Sci. Technol. **4**, 1151 (2014)
24. A.O. Abdelhamid, E.K.A. Abdelall, Y.H. Zakic, J. Heterocycl. Chem. **47**, 477 (2010)
25. S. Grosse, V. Mathieu, C. Pillard, S. Massip, M. Marchivied, C. Jarry, P. Bernard, R. Kiss, G. Guillaumet, Eur. J. Med. Chem. **84**, 718 (2014) **(and references sited therein)**.
26. A. Terada, K. Wachi, H. Myazawa, Y. Lizuka, K. Hagesawa, K. Tabata, Japanese Patent JP **07278148** (1995), Chem. Abst. **124**, 8700 (1996)
27. T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S.K. Guchhait, C.N. Kundu, U.S. Banerjee, P.V. Bharatam, J. Med. Chem. **54**, 5013 (2011)
28. G. Bhatia, P. Graczyk, A. Khan, D.P. Medland, H. Numata, H. Oinuma, V. Palmer, International Patent 310918 (2002). WO02081475 (A1) Chem. Abst. 137 (2002)
29. B. Frey, R. Hufton, M. Harding, A.G. Draffan, International Patent 446979 (2013). WO2013036994, Chem. Abst. 158 (2013)
30. K. Sata, T. Kawagishi, H. Kobayashi, Jpn. Kokai Tokyo 07,134,380(1995), Chem. Abst. 123, 183329q (1995)
31. J. Bailey, D. Rogers, WO 8602467 (1986), Chem. Abst. 105, 143476 (1986)
32. A. Barsy, E.A. El-Rady, J. Heterocycl. Chem. **43**, 523 (2006)

33. J. Khalafy, A. Poursattar Marjani, F. Salami, Tetrahedron Lett. **55**, 6671 (2014)
34. A. Rahmati, M. Eskandari-Vashareh, M. Alizadeh-Kouzehrash, Tetrahedron Lett. **69**, 4199 (2013)
35. A. Rahmati, M. Alizadeh-Kouzehrash, Synthesis **2011**, 2913 (2011)
36. S. Shawali, M.H. Abdelkader, M.A. Eltalbawy, Tetrahedron **58**, 2875 (2002)
37. E. Vanotti, F. Fiorentini, M. Villa, J. Heterocycl. Chem. **31**, 737 (1994)
38. L. Moafi, S. Ahadi, A. Bazgir, Tetrahedron Lett. **51**, 6270 (2010)
39. R. Akbarzadeh, T. Amanpour, A. Bazgir, Tetrahedron Lett. **70**, 8142 (2014)
40. Y. Tominaga, Y. Honkawa, M. Hara, A. Hosomi, J. Heterocycl. Chem. **27**, 775 (1990)
41. K. Groebke, L. Weber, F. Mehlin, Synlett 1998, 661 (1998)
42. H. Bienayme, K. Bouzid, Angew. Chem. **110**, 2349 (1998)