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ZSM-5-SO_3H as an efficient catalyst for the one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5- tetrasubstituted imidazoles under solvent-free conditions

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A simple one-pot three-component synthetic method is reported for the synthesis of 2,4,5-trisubstituted imidazole by three-component cyclocondensation of benzil, aromatic aldehydes and ammonium acetate under solvent-free conditions in the presence of ZSM-5-SO_3H as a catalyst. Moreover, the utility of this protocol was further explored for the one-pot, four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles from benzil, aromatic aldehydes, primary amines and ammonium acetate in good to high yield and purity.

Keywords: ZSM-5-SO_3H; 2,4,5-trisubstituted imidazoles; 1,2,4,5-tetrasubstituted imidazoles; Solvent-free.

Multi-component reactions (MCRs) have proved to be remarkably successful in generating products in a single synthetic operation. These reactions are classified in various ways based on the number of components involved in the reaction or their intrinsic variability. Nowadays organic chemical syntheses involving multi-component condensation strategy attained greater value, as the target molecules are often obtained in a single step rather than multiple steps, which minimizes the tedious work-up procedures and environmentally hazardous wastes [1].

The imidazole ring system is a vital heterocyclic nucleus found in a large number of natural products and pharmacologically active compounds. These compounds are known to have several therapeutic applications such as antimicrobial [2], antitubercular [3], cytotoxic [4], anti-inflammatory [5], and anticancer [6] activities. Several methods have been reported for the construction of this important structure. The most common method for preparation of these compounds involves three- and four-component condensations of a 1,2-diketone derivative with an aldehyde, ammonium acetate and primary amine using acidic conditions, such as zeolite [7], $NaHSO_4$–SiO_2 [8], $HClO_4$-SiO_2 [9], $FeCl_3$-$6H_2O$ [10], BF_3-SiO_2 [11], trifluroacetic acid [12], zeolite supported reagents [13], dicationic magnetic ionic liquid [14], MCM-41 or *p*-TsOH [15], 1-butyl-3-methylimidazolium bromide [16], silica-bonded propylpiperazine-*N*-sulfamic [17], *N*-methyl-2-pyrrolidonium hydrogen sulfate [18], and DABCO [19]. These methods are suitable for certain synthetic conditions; however, many of these procedures suffer from one or more disadvantages such as the use of expensive reagents, long reaction times, tedious separation procedures, and large amounts of catalyst loadings which in turn result in the generation of a large amount of wastes into the environment. Therefore, the development of mild, generalized and environmentally friendly approaches to overcome these shortcomings still remains an ongoing challenge for the synthesis of highly substituted imidazoles.

Solid acids are beginning to play a significant role in the greening of chemicals manufacturing processes. Recently, in continuation of our studies on solid acid catalysts [20], ZSM-5-SO_3H was synthesized for the first time in our group and was used in acylation of aldehydes [21] and Mannich reaction [22]. Based on these findings, we report here a simple approach for the synthesis of 2,4,5-trisubstituted imidazole (scheme 1) and 1,2,4,5-tetrasubstituted imidazoles (scheme 2) by the condensation of benzil, aldehydes, ammonium acetate and primary amines using ZSM-5-SO_3H as a mild heterogeneous catalyst.

To optimize the reaction conditions including solvents, molar ratios and temperature for the synthesis of 2,4,5-trisubstituted imidazoles, the reaction of benzil, 4-chlorobenzaldehyde and ammonium acetate was chosen as a model reaction. In order to determine the most appropriate choice of solvent system, we have screened solvents such as methanol, ethanol, acetonitrile and also used solvent-free conditions. Even though the reactions in ethanol led to a high yield of the product in shorter reaction times, the maximum yield was

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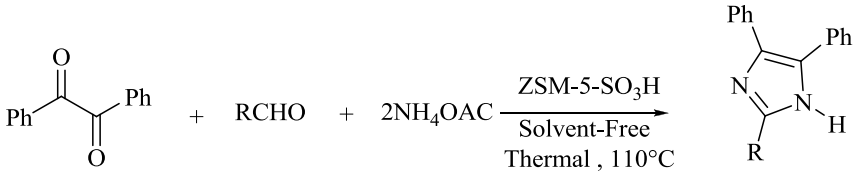
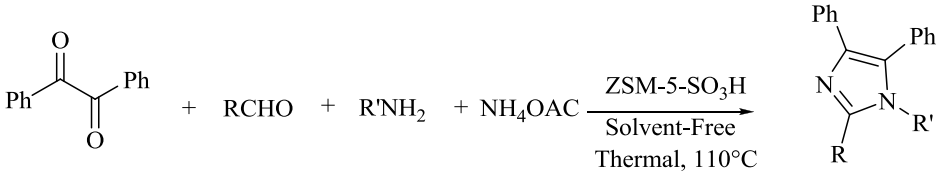
obtained under solvent-free conditions (Table 1, entry 4). Also, the reaction was examined at 50, 80 and 110 ˚C under solvent-free conditions (Table 1, entries 4-6). The results demonstrated that the yield at 110˚C was better than those at the other temperatures. The effect of catalyst amount on the yield of reaction was also studied (Table 1, entries 4 and 7-10). When the amount of the catalyst was increased from 0.01 g to 0.03 g, the yield increased from 50 % to 90 %. Higher amounts of the catalyst did not further improve the yields. In the absence of the catalyst, the reaction proceeded sluggishly (Table 1, entry 11). So, the optimum conditions were chosen as follows: benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (7 mmol) and ZSM-5-SO_3H (0.03 g), heating at 110^{o}C under solvent-free conditions.

We next examined a wide variety of aldehydes to establish the scope of this catalytic transformation (Table 2). Several aromatic aldehydes bearing electron donating and electron withdrawing substituents were subjected to this one-pot, three-component cyclocondensation to furnish 2,4,5-trisubstituted imidazoles in good to high yields. Various functional groups were found to be compatible under the reaction conditions. In general, the reactions were clean and no side products were detected. The aliphatic aldehydes lead to the corresponding imidazoles in lower yields in comparison to aromatic ones.



Scheme 1. ZSM-5-SO_3H catalyzed synthesis of 2,4,5-trisubstituted imidazoles



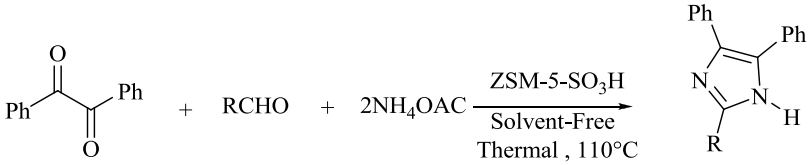
Scheme 2. ZSM-5-SO_3H catalysed synthesis of 1,2,4,5-tetrasubstituted imidazoles

Table 1. Synthesis of imidazole under different conditions [a]

Entry	Solvent	ZSM-5-SO_3H (g)	Temperature (^{o}C)	Time (min)	Yield (%)[b]
1	MeOH	0.03	65	170	33
2	EtOH	0.03	78	140	71
3	CH_3CN	0.03	81	200	51
4	Solvent-free	0.03	110	90	90
5	Solvent-free	0.03	50	90	56
6	Solvent-free	0.03	80	90	68
7	Solvent-free	0.01	110	90	50
8	Solvent-free	0.02	110	90	76
9	Solvent-free	0.06	110	90	90
10	Solvent-free	0.1	110	90	90
11	Solvent-free	-	110	240	20

[a] 4-Chlorobenzaldehyde (1.0 mmol), benzil (1.0 mmol) and ammonium acetate (7.0 mmol)
[b] Isolated yield

Table 2. Synthesis of 2,4,5-trisubstituted imidazoles using ZSM-5-SO_3H as a catalyst



Entry	Compd.	**R**	Time (min)	Yield [a] (%)	M.p. (°C) Found	M.p. (°C) Reported [Ref.]
1	1a	4-HOC_6H_4	120	71	235-239	233-234 [23]
2	1b	4-$MeOC_6H_4$	90	85	219-222	222-223 [23]
3	1c	4-ClC_6H_4	90	90	265-268	262-264 [18]
4	1d	C_6H_5	130	62	269-272	267-269 [18]
5	1e	4-$CH_3C_6H_4$	85	86	224-228	229-232 [27]
6	1f	4-$O_2NC_6H_4$	100	73	240-243	242-243 [23]
7	1g	3-$O_2NC_6H_4$	110	65	261-264	265-267[18]
8	1h	2,4-$Cl_2C_6H_3$	100	76	174-176	176-178 [18]
9	1i	3-ClC_6H_4	95	81	284-287	287-289 [18]
10	1j	$CH_3CH_2CH_2$	150	59	277-279	277-278 [23]

[a] Isolated yield

The same reaction conditions were applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles *via* one-pot, four-component condensation of benzyl (1 mmol), an aldehyde (1 mmol), a primary amine (1 mmol) and ammonium acetate (6 mmol) in the presence of 0.02 g of catalyst (Table 3). The substrate scope of the reaction was then evaluated by varying differently substituted aldehydes and primary amines including both electron-donating and electron-withdrawing groups. The use of a heterocyclic amine such as aminothiazole leads to the corresponding imidazole in high yield and purity.

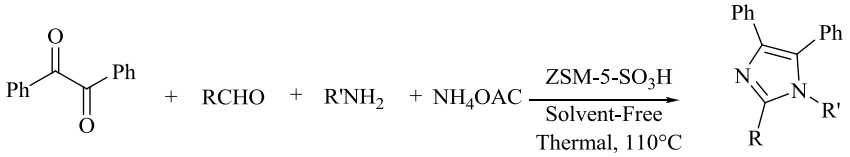
To our delight, the 1,2,4,5-tetrasubstituted imidazoles were obtained in good to high yields and no side products, for example, 2,4,5-trisubstituted imidazoles, were formed.

To show the merits of the present work in comparison with reported results in the literature, we compared ZSM-5-SO_3H with some reported heterogeneous catalysts in the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles. As shown in Tables 4 and 5, ZSM5-SO_3H acts as a suitable catalyst with respect to reaction times, yields of the products, temperature under solvent-free conditions.

Finally, the reusability of the catalysts was studied. For this purpose the recovered catalyst from the experiment was washed with ethyl acetate (3×5 mL), then was dried in oven at 60°C and used in the reaction. The results show that the catalyst can be reused 3 times without any modification and no significant loss of activity/selectivity performance was observed.

In summary, an efficient and environmentally friendly approach was introduced for the synthesis of imidazole derivatives *via* condensation of benzil with various aromatic aldehydes, a primary amine and ammonium acetate using ZSM-5-SO_3H as a catalyst. The solvent-free conditions, simplicity of operation, easy work-up, lower catalyst amount and cost efficiency render this approach as an interesting alternative to the existing methods.

Table 3. Synthesis of 1,2,4,5-tetrasubstituted imidazoles using ZSM-5-SO_3H



Entry	Compd.	**R**	**R´**	Time (min)	Yield (%)	M.p. (°C) Found	M.p. (°C) Reported [Ref.]
1	2a	4-ClC_6H_4	4-$MeOC_6H_4$	50	94	182-185	180-183 [25]
2	2b	C_6H_5	4-ClC_6H_4	40	86	239-242	237-240 [25]
3	2c	4-HOC_6H_4	4-ClC_6H_4	30	85	203-207	207-210 [24]
4	2d	4-ClC_6H_4	4-ClC_6H_4	50	90	186-189	187-189 [28]
5	2e	4-ClC_6H_4	C_6H_5	30	78	158-160	163-165 [9]
6	2f	4-ClC_6H_4	4-$CH_3C_6H_4$	30	93	193-195	197-199 [18]
7	2g	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	55	64	168-170	167-170 [18]
8	2h	4-$MeOC_6H_4$	$CH_2C_6H_5$	50	73	162-167	164-165 [25]
9	2i	4-$CH_3C_6H_4$	C_6H_5	35	91	179-183	177-180 [26]
10	2j	4-HOC_6H_4	$CH_2C_6H_5$	55	79	235-238	232-235 [26]
11	2k	4-ClC_6H_4	aminothiazole	60	81	227-229	226-228 [24]
12	2l	C_6H_5	4-$CH_3C_6H_4$	30	90	165-167	168-170 [11]
13	2m	4-ClC_6H_4	$CH_2C_6H_5$	60	70	166-169	162-164 [23]
14	2n	C_6H_5	C_6H_5	40	85	218-220	220-221 [18]
15	2o	4-$O_2NC_6H_4$	C_6H_5	60	63	209-212	212-214 [24]
16	2p	4-HOC_6H_4	C_6H_5	55	77	284-289	281-283 [24]
17	2q	$CH(Me)_2$	C_6H_5	100	51	231-233	232-234 [25]

[a] Isolated yield

Table 4. Comparison of various catalysts with ZSM-5-SO_3H in the synthesis of 2,4,5-trisubstituted imidazoles from 4-chloro benzaldehyde, benzyl and ammonium acetate

Entry	Catalyst (g)	Solvent	Temperature (°C)	Time (min)	Yield (%)	Ref.
1	$InCl_3 \cdot 3H_2O$	MeOH	140	540	71	[23]
2	$NiCl_2 \cdot 6H_2O/Al_2O_3$	EtOH	80	360	80	[25]
3	ZSM-5	EtOH	80	60	80	[24]
4	Silica gel	Solvent-free	140	120	68	[18]
5	L-proline	MeOH	60	540	88	[25]
6	$Pb(NO_3)_2$	EtOH	80	300	52	[23]
7	ZSM-5-SO_3H	Solvent-free	110	90	90	This work

Table 5. Comparison of various catalysts with ZSM-5-SO_3H in the synthesis of 1,2,4,5-tetrasubstituted imidazole from benzaldehyde, benzil, 4-chloro aniline and ammonium acetate

Entry	Catalyst (g)	Solvent	Temperature (°C)	Time (min)	Yield (%)	Ref.
1	$InCl_3 \cdot 3H_2O$	MeOH	140	440	79	[23]
2	$Co(NO_3)_2$/MCM-41	Solvent-free	120	90	11	[13]
3	$Cu(NO_3)_2$/zeolite-HY	EtOH	70	180	53	[13]
4	$SnCl_4$	Solvent-free	140	120	60	[26]
5	$MgCl_2$	Solvent-free	140	120	50	[18]
6	$AlCl_3$	MeOH	60	120	53	[23]
7	$Cu(NO_3)_2$/zeolite-HY	MeOH	65	180	56	[13]
8	ZSM-5-SO_3H	Solvent-free	110	40	86	This work

EXPERIMENTAL

The chemicals were purchased from Merck and Aldrich and were used without additional purification. The products were characterized by comparison with authentic samples and by spectroscopy data (IR, ^{1}H NMR and ^{13}C NMR spectra). The NMR spectra were recorded on a Bruker BioSpin GmbH 400 MHz instrument. FT-IR spectra were recorded on a Perkin Elmer spectrometer. The yields refer to isolated products after purification.

Synthesis of Catalyst

Zeolite ZSM-5 was prepared under hydrothermal conditions with SiO_2/Al_2O_3 = 80. Sodium chloride (2.50 g) and aluminum sulfate (0.59 g) were dissolved at room temperature in distilled water (10.12 g) then 1.89 g tetrapropyl ammonium bromide (TPA), distilled water (7.12 g) and sulfuric acid (1.09 g) were added to this solution and stirred to dissolve completely. At the end 15.00 g of sodium silicate was added and the synthesis was carried out under stirring at room temperature for 1 h or more to obtain a milky homogeneous mixture. Then the mixture was moved to the reactor and kept at 110 ºC for 2 h and at 230 ºC for 5.5 h. The solution was filtered and washed with distilled water. Template removal was performed by calcination at 550 ºC for 6 h. ZSM-5-SO_3H was synthesized following the procedure previously reported by Zolfigol for the synthesis of silicasulfuric acid.

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles:

Aldehyde (1mmol) and ZSM-5-SO_3H (0.03 g) were ground in a mortar for a few seconds. Then, benzil (1 mmol) and ammonium acetate (7 mmol) were added to the mixture and heated at 110 ºC under solvent-free conditions. After completion of the reaction, monitored by TLC, the mixture was cooled to room temperature and ethyl acetate (30 mL) was added and the catalyst was separated by filtration. The organic layer was washed with water (15 mL) and dried over sodium sulfate. After evaporation of the solvent the product was purified by recrystallization from ethanol.

General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles:

Aldehyde (1 mmol) and ZSM-5-SO_3H (0.02 g) were ground in a mortar for a few seconds. Then, benzil (1 mmol), aryl amine (1 mmol) and ammonium acetate (6 mmol) were added to the mixture and heated at 110 ºC under solvent-free conditions. After completion of the reaction, monitored by TLC, the product was separated and purified as the above procedure.

Selected spectral data:

2-(4-chlorophenyl)-1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole (2a): Yield 94%, m.p. 182-185 ºC, IR (KBr, cm^{-1}): 3056, 1600 , 1510 ,1248; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.81 (s, 3H), 6.80 (d, 2H, J = 8.8 Hz), 6.97 (d, 2H, J = 8.8 Hz), 7.16 (d, 2H, J = 9.6 Hz), 7.21–7.32 (m, 8H), 7.41 (d, 2H, J = 9.3 Hz), 7.56 (d, 2H, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 55.4, 114.4, 126.7, 127.4, 128.1, 128.2, 128.4, 128.5, 129.1, 129.4, 129.6, 130.1, 130.5, 131.1, 131.4, 134.2, 134.3, 138.2, 145.9, 159.3;

2-(4-chlorophenyl)-1,4,5-triphenyl-1H-imidazole (2e): Yield 78%, m.p. 158-160 ºC, IR (KBr, cm^{-1}): 3058, 1595, 1490 ,1245; ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 7.19 (d, 2H, J = 8.0 Hz), 7.23–7.34 (m, 11H), 7.36 (d, 2H, J = 8.0 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 126.3, 126.6, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 129.1, 129.2, 129.8, 130.2, 131.1, 131.5, 133.1, 134.2, 136.4, 136.9, 144.8;

2-(4-chlorophenyl)-4,5-diphenyl-1-p-tolyl-1H-imidazole (2f): Yield 93%, m.p. 191-193 ºC, IR (KBr, cm^{-1}): 3045, 1606 , 1499 ,1248; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.36 (s, 3H), 6.94 (d, 2H, J = 8.0 Hz), 7.09 (d, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 8.0 Hz), 7.08–7.30 (m, 8H), 7.41 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.4 Hz).

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REFERENCES

1. J. Zhu, H. Bienayme (Eds), Multicomponent reactions, Wiley-VCH, Weinheim, 2005.
2. L. Nagarapu, A. Satyender, B. Rajashaker, K. Srinivas, P. R. Rani, K. Radhika, G. Subhashini, *Bioorg. Med. Chem. Lett.*, **18**, 1167 (2008).
3. P. Gupta, S. Hameed, R. Jain, *Eur. J. Med. Chem.*, **39**, 805 (2004).
4. J. Arrowsmith, S. A. Jennings, A. S. Clark, M. F. G. Stevens, *J. Med. Chem.*, **45**, 5458 (2002).
5. L. Navidpour, H. Shadnia, H. Shafaroodi, M. Amini, A. R. Dehpour, A. Shafiee, *Bioorg. Med. Chem.*, **15**, 1976 (2007).
6. C. Kus, G. Ayhan-Kilcigil, S. Ozbey, F. B. Kaynak, M. Kaya, T. Coban, B. Can-Eke, *Bioorg. Med. Chem.*, **16**, 4294 (2008).
7. A. Bamoniri, B.F. Mirjalili, S. Nazemian, N.Y. Mahabadi, *Bulg. Chem. Commun.*, **46**, *79* (2014).
8. A. R. Karimi, Z. Alimohammadi, J. Azizian, A. A. Mohammadi, M. R. Mohammadizadeh, *Catal. Commun.*, **7**, 728 (2006).
9. S. Kantevari, S. V. N. Vuppalapati, D. O. Biradar, L. Nagarapu, *J. Mol. Catal. A: Chem.*, **266**, 109 (2007).
10. M. M. Heravi, F. Derikvand, M. Haghighi, *Monatsh. Chem.*, **139**, 31 (2008).
11. B. Sadeghi, B. B. F. Mirjalili, M. M. Hashemi, *Tetrahedron Lett.*, **49**, 2575 (2008).
12. M. R. Mohammadizadeh, A. Hasaninejad, M. Bahramzadeh, *Synth. Commun.*, **39**, 3232 (2009).
13. K. Sivakumar, A. Kathirvel, A. Lalitha, *Tetrahedron Lett.*, **51**, 3018 (2010).
14. B. Mombani Godajdar., A. R. Kiasat, *Iran. J. Catal.*, **3**, 229 (2013).
15. R. Hekmat Shoar, G. Rahimzadeh, F. Derikvand, M. Farzaneh, *Synth. Commun.*, **40**, 1270 (2010).
16. A. Hassaninejad, A. Zare, M. Shekouhy, J. A. Rad, *J. Comb. Chem.*, **12**, 844 (2010).
17. K. Niknam, A. Deris, F. Naeimi, F. Majleci, *Tetrahedron Lett.*, **52**, 4642 (2011).
18. H. R. Shaterian, M. Ranjbar, *J. Mol. Liq.*, **160**, 40 (2011).
19. S. Narayana Murthy, B. Madhav, Y. V. D. Nageswar, *Tetrahedron Lett.*, **51**, 5252 (2010).
20. (a) A. R. Massah, B. Asadi, M. Hoseinpour, A. Molseghi, R. J. Kalbasi, H. J. Naghash, *Tetrahedron*, **65**, 7696 (2009). (b) H. Adibi, A. R. Massah, M. B. Majnooni, S. Shahidi, M. Afshar, R. Abiri, H. J. Naghash, *Synth. Commun.*, **40**, 2753 (2010). (c) A. R. Massah, H. Adibi, R. Khodarahmi, R. Abiri, M. B. Majnooni, S. Shahidi, B. Asadi, M. Mehrabi, M. A. Zolfigol, *Bioorg. Med. Chem.*, **16**, 5465 (2008); (d) A. R. Massah, M. Dabagh, S. Shahidi, H. J. Naghash, A. R. Momeni, H. Aliyan, *J. Iran Chem. Soc.*, **6**, 405 (2009); (e) F. Kazemi, A. R. Massah, H. J. Naghash, *Tetrahedron*, **63**, 5083 (2007).
21. A. R. Massah, R. J. Kalbasi, A. Shafiei, *Monatsh. Chem.*, **143**, 643 (2012).
22. A. R. Massah, R. J. Kalbasi, N. Samah, *Bull. Korean Chem. Soc.*, **32**, 1703 (2011).
23. S. D. Sharma, P. Hazarika, D. Konwar, *Tetrahedron Lett.*, **49**, 2216 (2008).
24. A. Teimouri, A. N. Chermahini, *J. Mol. Catal. A: Chem.*, **346**, 39 (2011).
25. S. Samai, G. C. Nandi, P. Singh, M. S. Singh, *Tetrahedron*, **65**, 10155 (2009).
26. F. K. Behbahani, T. Yektanezhad, *Monatsh. Chem.*, **143**, 1529 (2012).
27. J. Safari, Z. Zarnegar, *Iran J. Catal.*, **3**, 121 (2012).
28. L. Nagarapu, S. Apuri, S. Kantevari, *J. Mol. Catal. A: Chem.*, **266**, 104 (2007).

ZSM-5-SO_3H КАТО ЕФИКАСЕН КАТАЛИЗАТОР ЗА ЕДНО-СТАДИЙНАТА СИНТЕЗА НА 2,4,5-ТРИ-ЗАМЕСТЕНИ И 1,2,4,5- ТЕТРА-ЗАМЕСТЕНИ ИМИДАЗОЛИ В ОТСЪСТВИЕ НА РАЗТВОРИТЕЛ

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(Резюме)

В работата се съобщава за едно-стадиен три-компонентен метод за синтезата на 2,4,5-тризаместен имидазол чрез три-компонентна цикло-кондензация на бензил-ароматни алдехиди и амониев ацетат в отсъствие на разтворител в присъствие на ZSM-5-SO_3H като катализатор. Освен това прилагането на този протокол е изпитан за едно-стадийна четири-компонентна синтеза на 1,2,4,5-тетразаместени имидазолови производни от бензил, ароматни алдехиди, първични амини и амониев ацетат с високи добиви и чистота.