J. Chem. Sci. Vol. 124, No. 3, May 2012, pp. 717–722.

A novel polymeric catalyst for the one-pot synthesis of 2,4,5-triaryl-1H-imidazoles

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MS received 8 August 2011; revised 29 November 2011; accepted 20 January 2012

Abstract. An efficient synthesis of 2,4,5-trisubstituted imidazoles is achieved by three component cyclocondensation of benzil or benzoin, aldehyde and ammonium acetate by using novel polymeric catalyst [poly(AMPS-co-AA)] under solvent-free conditions. The key advantages of this process are high yields, shorter reaction times, easy work-up, purification of products by non-chromatographic method and the reusability of the catalyst.

Keywords. 2,4,5-Trisubstituted imidazoles; solvent-free synthesis; multicomponent reaction; poly(AMPS-co-AA); heterogeneous catalysts.

1. Introduction

Multicomponent reactions (MCRs) have drawn great interest in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity.[1,2] MCRs have contributed in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery.[3,4] The imidazole nucleus is a fertile source of biologically important molecules. Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes. They are well-known as inhibitors of P38MAP kinase, fungicides, herbicides, antiinflammatory agents, antithrombotic agents, plant growth regulators and therapeutic agents. In addition, they are used in photography as photosensitive compounds. Some substituted triarylimidazoles are selective antagonists of the glucagons receptor and inhibitors of IL-1 biosynthesis.[5] Radziszewski and Jaap proposed the first synthesis of the imidazole core in 1882, starting from 1,2-dicarbonyl compounds, aldehydes and ammonia to obtain 2,4,5-triphenylimidazole.[6,7] There are several methods for the synthesis of 2,4,5-triarylimidazoles using $ZrCl_4$,[8] zeolites HY/silica gel,[9] $NaHSO_3$,[10] sulphanilic acid,[11] iodine,[12] ceric ammonium nitrate,[13] oxalic acid,[14] ionic liquids[15] and also by microwave irradiation using acetic acid.[16] Each of the above methods for this reaction has its own merits, while some of the methods are plagued by the limitations of poor yield, longer reaction time, difficult work-up and effluent pollution.[5] Therefore, the development of a new mild method to overcome these disadvantages still remains a challenge for organic chemists. One of the aims we have in mind is to introduce a new catalyst for synthesis of 2,4,5-trisubstituted imidazoles with cost effectiveness and mild condition in high yields. In 1963, Merrifield introduced a modified technique that overcame the problems associated with classical multistep synthesis. This technique has been used in the production of large amount of products. However, recently, the chemistry of functional polymers has received great attention and became a practical method for the efficient preparation of novel chemical libraries.[17] Polymeric reagents have recently been developed for use in simple processes such as epoxidation, oxidation, acylation, halogenation, and Wittig reactions. In all of these applications, the advantages of the selectivity, insolubility, and reusable capacity of the polymeric reagent

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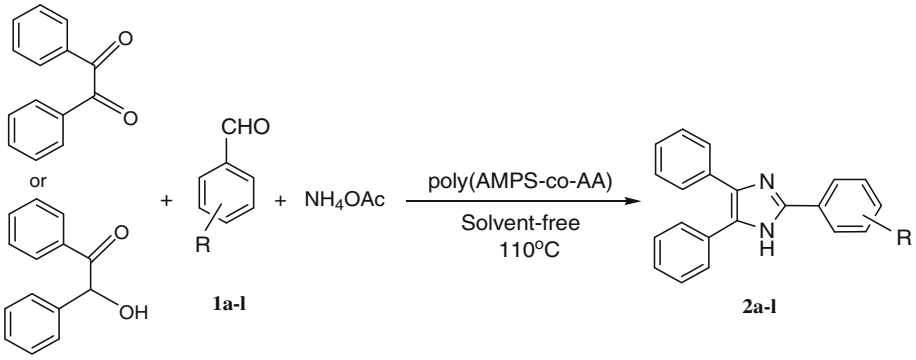

Figure 1. Crosslinked poly (AMPS-co-AA) catalysed synthesis of 2,4,5-trisubstituted imidazole.

are taken.[18] Polymers are a large family of compounds that provide a variety of compositions and properties that can be useful in catalysis. Insoluble polymers offer suitable substrates for the heterogenization of homogeneous catalysis, but even the attachment of catalysts to soluble polymers have advantages, since being macromolecules, these polymers can easily be separated from the reaction mixture by the addition of a co-solvent or by ultrafiltration.[19]

With these assumptions, we report here the solvent-free synthesis of 2,4,5-trisubstituted imidazoles using poly(2-acrylamido-2-methyl propane sulphonic acid) (AMPS) crosslinked with *N,N′*-methylene bisacrylamide (MBA) as a novel catalyst under classical heating (figure 1).

We examined a wide variety of aromatic aldehydes with various substituents to establish the catalytic importance of this catalyst for this reaction. A wide range of *ortho*-, *meta*- and *para*-substituted aromatic aldehydes undergo this one-pot multicomponent synthesis with benzil or benzoin and ammonium acetate to afford 2,4,5-trisubstituted imidazoles in good yields.

2. Experimental

Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were recorded with a Varian 3100 FTIR spectrometer. CHN analyses were performed on Exeter Analytical Inc. 'Model CE-400 CHN Analyzer'. ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER DRX-400 AVANCE spectrometer at 298 °K and 75.47 MHz, respectively. NMR spectra were obtained on solutions in DMSO-d_6. All the products were known compounds,[20–26] which were characterized by IR and ^{1}H NMR spectral data and their melting point compared with literature reports.

3. General procedure

3.1 *Preparation and reusability of the crosslinked poly (AMPS-co-AA) catalyst*

Crosslinked poly (AMPS-co-AA) was prepared according to the literature,[27] by polymerization of 2-acrylamido-2-methyl-1-propane sulphonic acid (AMPS) and acrylic acid (AA) as the monomers in water, in the presence of a crosslinking agent *N,N′*-methylene bisacrylamide (MBA) and potassium persulphate (KPS) as a free radical initiator (figure 2). The structure of the polymer was characterized by FTIR analysis. When the crosslinked poly (AMPS-co-AA) was used in the reaction and the reaction was completed, the polymeric catalyst was separated by simple filtration by diluting with hot ethanol and then oven dried in 110 °C for 24 h. The recycled catalyst was employed consecutively for three reactions and no significant loss in its efficiency was observed.

3.2 *General procedure for preparation of* **2a–l**

A mixture of aldehyde (1 mmol), benzil or benzoin (1 mmol), ammonium acetate (5 mmol) and crosslinked poly (AMPS-co-AA) (0.03 g), as a catalyst, in a 20 ml glass tube was stirred at 110 °C for 25–35 min. After completion of the reaction, appropriate amounts of hot EtOH (96%) was added and the mixture stirred for 10 min. then, the catalyst separated by filtration. The filtrate was concentrated *in vacuo* to remove the ethanol. The residue was washed with cold water and crystallized from hot ethanol to afford the pure products.

3.3 *Selected spectral data*

3.3.a. *2,4,5-Triphenyl-1H-imidazole* (**2a**): Yield: (92%, 272 mg); Mp 273–275°C; FTIR (KBr, cm^{-1}): 3451,

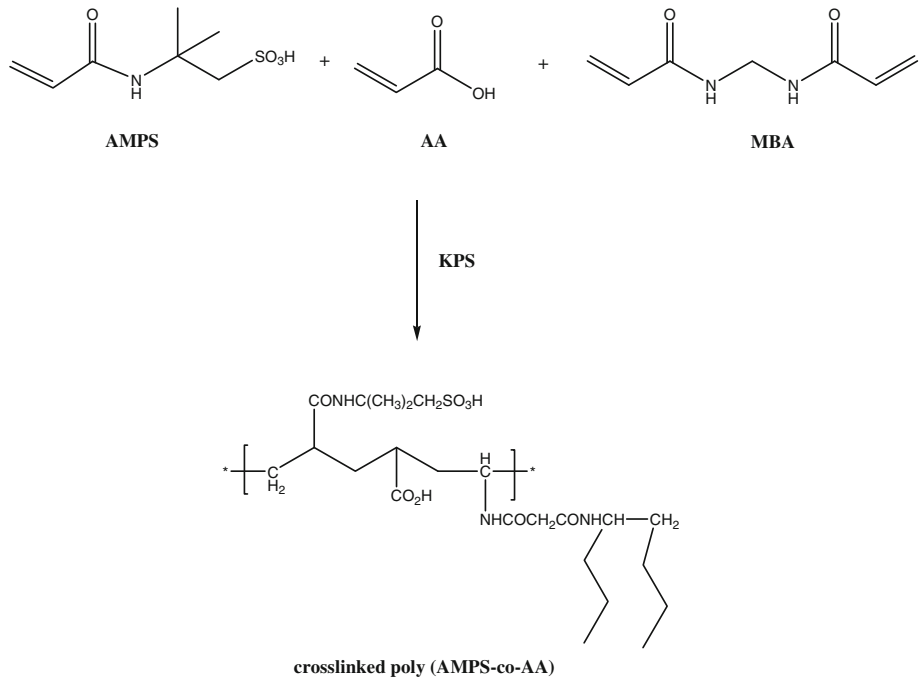

Figure 2. Preparation of crosslinked poly (AMPS-co-AA).

2856, 1636, 1490; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H), 8.09 (d, J = 7.7 Hz, 2H), 7.56–7.22 (m, 13H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 145.6, 137.2, 135.2, 131.2, 130.4, 128.7, 128.5, 128.3, 128.2, 127.8, 127.2, 126.6, 125.3; Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.18; H, 5.49; N, 9.33.

3.3.b. *2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole* (**2b**): Yield: (95%, 313 mg); Mp 264–266°C; FTIR (KBr, cm^{-1}): 3452, 3065, 1635, 1323; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (s, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.56–7.23 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 146.3, 130.3, 129.9, 129.2, 128.5, 127.4, 127.0, 126.4, 125.5, 125.2, 123.3, 116.3; Anal. Calcd for $C_{21}H_{15}N_2Cl$: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.20; H, 4.61; N, 8.41.

3.3.c. *4,5-Diphenyl-2-p-tolyl-1H-imidazole* (**2c**): Yield: (85%, 263 mg); Mp 231–232°C; FTIR (KBr, cm^{-1}): 3449, 3034, 1611, 1495, 1320; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.59 (s, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.54–2.21 (m, 12H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 145.6, 137.6, 136.9, 135.2, 131.1, 129.2, 128.6, 128.3, 128.1, 127.9, 127.6, 127.0, 126.4, 125.1, 20.8; Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.23; H, 5.79; N, 8.97.

3.3.d. *2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole* (**2d**): Yield: (85%, 277 mg); Mp 230–233°C; FTIR (KBr, cm^{-1}): 3425, 3029, 2956, 1610, 1495, 1249; ^{1}HNMR (400 MHz, DMSO-d_6): δ 12.50 (s, 1H), 8.03 (d, J = 8.5 Hz, 2H), 7.50–7.05 (m, 12H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.5, 145.7, 128.4, 127.7, 126.8, 123.1, 114.1, 55.2; Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.90; H, 5.51; N, 8.63.

3.3.e. *4-(4,5-Diphenyl-1H-imidazol-2-yl)-phenol* (**2e**): Yield: (90%, 280 mg); Mp 265–267°C; FTIR (KBr, cm^{-1}): 3590, 3454, 3284, 3064, 1701, 1283; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.40 (s, 1H), 9.75 (s, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.54–7.21 (m, 10H), 6.86 (d, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.7, 146.1, 136.6, 135.4, 131.3, 128.6, 128.3, 127.5, 127.3, 127.0, 126.8, 126.3, 121.6, 115.4; Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.79; H, 5.22; N, 8.91.

3.3.f. *2-(4-Fluorophenyl)-4,5-diphenyl-1H-imidazole* (**2f**): Yield: (86%, 270 mg); Mp 250–252°C; FTIR (KBr, cm^{-1}): 3316, 2993, 2470, 1660, 1210, 1169, 874, 719, 639; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 8.28 (d, J = 7.1 Hz, 2H), 7.55–7.03 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.4, 137.3, 131.1, 129.8, 128.9, 127.7, 127.2, 126.6, 125.9, 125.5, 124.1,

Table 1. Optimization one-pot synthesis of trisubstituted imidazoles under classical heating conditions.[a]

Entry	poly(AMPS-co-AA) (g)	T(°C)	Time(min)	Yield(%)
1	0.01	100	60	50
2	0.01	110	55	56
3	0.01	120	45	70
4	0.01	130	40	75
5	0.02	110	50	70
6	0.02	120	30	78
7	0.02	130	35	80
8	0.03	110	25	95
9	0.03	120	25	95
10	0.03	130	30	85
11	0.04	110	30	90

[a]Benzil (1 mmol), 4-chloro benzaldehyde (1 mmol) and ammonium acetate (5 mmol)

117.4; Anal. Calcd for $C_{21}H_{15}N_2F$: C, 76.27; H, 4.54; N, 8.41. Found: C, 76.22; H, 4.60; N, 8.43.

3.3.g. *2-(2-Methoxyphenyl)-4,5-diphenyl-1H-imidazole* (**2g**): Yield: (85%, 277 mg); Mp 212–213°C; FTIR (KBr, cm^1): 3430, 3038, 2950, 1615, 1495; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82, (s, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.53–7.07 (m, 13H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.2, 146.2, 128.3, 127.5, 125.4, 123.8, 115.4, 55.3; Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.90; H, 5.63; N, 8.51.

3.3.h. *2-(3-Nitrophenyl)-4,5-diphenyl-1H-imidazole* (**2i**): Yield: (85%, 289 mg); Mp 301–302°C; FTIR (KBr, cm^{-1}): 3448, 3068, 1526, 1350; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (s, 1H), 8.90 (s, 1H), 8.56 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.56–7.30 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.4, 143.4, 131.8, 131.2, 130.4, 128.7, 128.4, 127.1, 122.6, 119.4; Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.84; H, 4.47; N, 12.39.

4. Results and discussion

Several methods are used in the synthesis of these trisubstituted imidazoles and their derivatives. In addition, the synthesis of these heterocycles has been usually carried out in polar organic solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed of. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in huge amounts for organic reactions have posed a serious threat to the environment.[28] Thus, design of solvent-free catalytic reaction has received more attention in recent times in the area of green synthesis.[29]

Efficiency of this reaction is mainly affected by the amount of catalyst, temperature and reaction time. For getting the best conditions, initially we started the condensation of benzil (1 mmol), 4-chloro benzaldehyde (1 mmol) and ammonium acetate (5 mmol) in the presence of crosslinked poly (AMPS-co-AA) (0.01 g) as a catalyst at 100°C for 55 min, which led to low yield

Table 2. Synthesis of 2,4,5-triaryl-1H-imidazoles **(2a–l)** using crosslinked poly(AMPS-co-AA) (0.03 g) under solvent-free conditions.

Products[a]	*R*	Time (min)		Yields (%)[b]		Mp/ °C	
		Benzil	Benzoin	Benzil	Benzoin	Found	Reported
2a	4-H	25	25	92	90	273–275	272–274[20]
2b	4-Cl	25	25	95	90	264–266	262–264[20]
2c	4-CH_3	25	30	85	80	231–232	230–232[21]
2d	4-OMe	30	35	85	80	230–233	228–231[20]
2e	4-OH	35	35	90	85	265–267	268–270[22]
2f	4-F	35	35	86	80	250–252	250–251[23]
2g	2-OMe	30	30	85	85	212–213	210–211[22]
2h	3-Br	30	30	90	85	232–233	231–233[24]
2i	3-NO_2	35	35	85	80	301–302	>300[24]
2j	2-CH_3	30	35	90	88	201–204	205–207[25]
2k	4-Br	25	25	92	85	264–266	263–265[21]
2l	3,4-diOMe	30	30	85	80	217–219	216–218[26]

[a]All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H- and ^{13}C-NMR spectral analysis and by direct comparison with authentic materials; [b]Isolated yields

(50%) of 2,4,5-trisubstituted imidazole. To enhance the yield of the desired product the temperature of the reaction was increased to 130°C. With increasing the temperature, the reaction time decreased and the productivity of the reaction increased but was not very high. Hence, it was thought worthwhile to carry out the reaction in the presence of higher amount of the catalyst. As indicated in table 1, Maximum yield was obtained (95%) when the reaction was loaded with 0.03 g of the catalyst at 110°C. A further increasing of catalyst loading did not affect the yield (entry 11, table 1).

After optimizing the conditions, we applied this catalyst for synthesis of trisubstituted imidazoles by using different aromatic aldehydes with a wide range of *ortho*-, *meta*- and *para*-substitutions under solvent-free classical heating conditions to establish the catalytic importance of crosslinked poly(AMPS-co-AA) for this reaction.

Generally, the synthetic procedure involves stirring the mixture of aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (5 mmol) and crosslinked poly (AMPS-co-AA) (0.03 g) for 25–35 min at 110°C. The corresponding results are given in table 2. We found that the reaction proceeded very efficiently either electron-releasing or electron-withdrawing substituents on aryl ring of aldehyde.

Also, due to direct use of benzoin rather than benzil in the synthesis of imidazoles a significant improvement

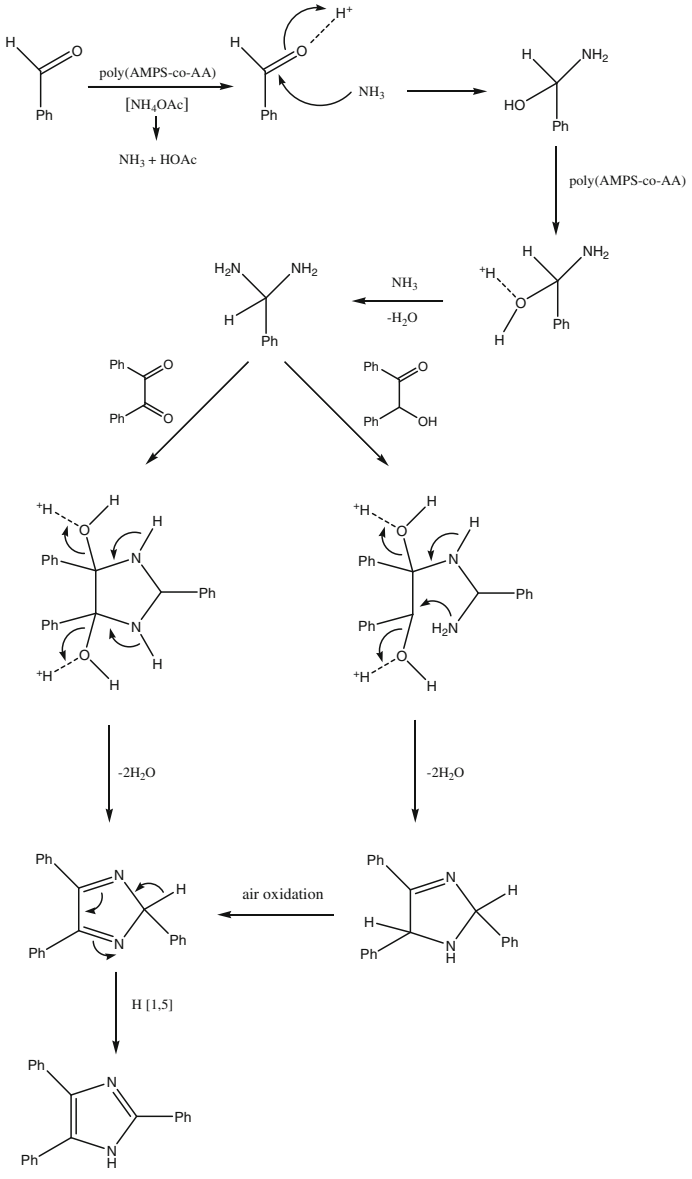

Figure 3. Probable mechanism for the formation of triarylimidazoles using benzil or benzoin, ammonium acetate, aromatic aldehydes and poly (AMPS-co-AA) as catalyst.

in the synthesis toward the greener chemistry is represented. We have repeated the reaction with benzoin instead of benzil and the desired product has been efficiently produced. As indicated in table 2, when we used benzoin instead of benzyl, the reaction time increased and also the yield of the reaction decreased partially.

Possible mechanism for the crosslinked poly (AMPS-co-AA) catalysed synthesis of trisubstituted imidazoles has been given in figure 3.[30] In summary, this paper describes a convenient and efficient process for the solvent-free synthesis of trisubstituted imidazoles through the three-components coupling of benzil or benzoin, aldehydes and ammonium acetate using crosslinked poly(AMPS-co-AA) as a catalyst. Reaction profile is very clean and no by-products are formed. All the synthesized imidazoles have been characterized on the basis of elemental and spectral studies. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of trisubstituted imidazoles of biological and medicinal importance.

5. Conclusion

We have been able to introduce an efficient and environmentally friendly approach for the synthesis of biologically active trisubstituted imidazoles via condensation of benzil or benzoin with various aromatic aldehydes and ammonium acetate using crosslinked poly (AMPS-co-AA) as a catalyst. High yields, easy work-up, purification of compounds by non-chromatographic method (crystallization only) and the reusability of the catalyst are the key advantages of this method.

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