ORIGINAL ARTICLE

A C G publications

Org. Commun. 15:1 (2022) 44-58

organic communications

Mandelic acid: an efficient and green organo-catalyst for synthesis of 2,4,5-trisubstituted Imidazoles under solvent-free conditions

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(Received January 30, 2022; Revised February 11, 2022; Accepted March 06, 2022)

Abstract: A simple and efficient general procedure has been developed for the synthesis of three-component reaction methodology of 2,4,5-trisubstituted imidazoles by using benzil, ammonium acetate and various aromatic aldehydes. In this methodology, mandelic acid is used as a novel and efficient organo-catalyst in catalytic amount under solvent-free conditions for preparation of variety of 2,4,5-trisubstituted imidazoles derivatives in excellent yields. All products have been characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. This method provides versatile advantages of organo-catalyst such as economical, nontoxic, highly stable, readily and easily available as well as solvent-free reaction conditions.

Keywords: 2,4,5-trisubstituted imidazoles; benzil; ammonium acetate; mandelic acid; organo-catalyst; solvent-free.

1. Introduction

In recent year, multicomponent reactions (MCRs) have enormous involvement occurred in convergent synthesis for preparation of important organic molecules in pharmaceutical as well as agrichemical industries. In MCRs, more than two compounds are involved in one-pot processes to synthesize various organic compounds in shorter reaction time with high yields and high selectivity[1-4]. Certainly, MCRs have been used widely to form organic as well as heterocyclic complex molecules, which has not easy to get through traditional linear methods.

Imidazole[5-7] is an important heterocyclic system gained remarkable attention due to their diverse application in pharmaceutical[8-13] and agrochemical industries[14-16]. In addition to this, substituted imidazole derivatives are broadly used in emerging research area like preparation of dyes for solar cells[17] and other optical materials[18-23], as well as synthesis of ionic liquids[24], functional materials[25], and organo-catalyst[26]. Due to the high level of interest in substituted imidazoles, a number of methods have been developed for synthesis of 2,4,5-trisubstituted imidazole derivatives by using various catalysts such as, Homogeneous Lewis acids[27-42], Heterogeneous Lewis acids[43-61], Heterogeneous Brønsted acids[62-79], Organo-catalysts[80-97], Phase transfer catalysts[98-102], Polymer supported catalysts[103-104], Ionic liquids[105-116], as well as different Solvent systems[117-124]. In similar manner, some of the new techniques such as microwave irradiation[125-137], ultrasound irradiation[138-142], with various catalysts have been also reported. Many of the reported methods involve one or two limitations such as, use of expensive or toxic reagents, harsh reaction conditions, extended reaction times, tedious workup procedures and low yields. Therefore, there is scope to develop new efficient and environmental benign green chemical processes, which are major challenges for researcher in organic synthesis.

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The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © January-March 2022 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.118.22.01.2341
Available online: March 12, 2022

In the past years, the use of organo-catalyst has received considerable attention due to its inexpensive, non-toxicity and readily available for the synthesis various organic and heterocyclic molecules[143-144]. Among many others organo-catalyst, mandelic acid is mild, non-toxic, cost-effective, highly stable and commercially available catalyst which is used for the preparation of chiral auxiliaries in stereoselective syntheses[145-148]. Nowdays, for the green and efficient practical chemical reaction condition, Kaur et al. has been reported some methodologies by using mandelic acid as organo-catalyst[149-151].

In continuation of our ongoing research towards the development of novel methodologies for organic transformation using alternative protocols[152-154] and by considering the significance of 2,4,5-trisubstituted imidazoles, herein we wish to report, a simple, efficient and environmental friendly procedure for the synthesis of 2,4,5-trisubstituted imidazoles using inexpensive mandelic acid as organo-catalyst under solvent-free conditions.

2. Experimental

2.1. Chemical Material and Apparatus

Reagents and solvents were purchased from commercially and used without purification. ^{1}H NMR spectra were recorded on Gemini-300 spectrometer in DMSO-d_6 using TMS as an internal standard and IR spectra were recorded on a Bruker FT-IR spectrophotometer using neat or KBr disk. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer with operating at 70 eV. Melting points were determined with Buchi R-535 apparatus are uncorrected.

2.2. General Procedure

The mixture of benzil (1 mmol), , aromatic aldehydes (1 mmol), and ammonium acetate (2 mmol) were heated in presence of mandelic acid (20 % mol) under solvent-free condition at 120 °C by using oil bath. After completion of reaction monitored by thin layer chromatography, 10 ml water was added to the mixture and stirred for 5 minutes to get solid residue. The obtained residue was filtered, and washed with excess water. The resulting crude product was crystallized with ethanol. All the pure products were confirmed by their spectroscopy data.

2.3. Spectral Data of Synthesized Compounds

*2,4,5-triphenyl-1H-imidazole (**4a**)*: White solid, m.p. 270-272 °C ($^{Lit[81]}$ 267-269 °C); IR (KBr): ῡ= 3454, 3045, 2870, 1631, 1490, 1461, 1126, 1072 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 12.73 (s, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.65-7.24 (m, 13H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ= 145.5, 137.5, 135.2, 131.8, 130.8, 129.3, 129.0, 128.5, 128.2, 127.8, 126.4, 125.3 ppm; ESIMS: *m/z*: 297 (M^{+1})**.**

*4,5-diphenyl-2-(p-tolyl)-1H-imidazole (**4b**)*: White solid, m.p. 232-234 °C ($^{Lit.[81]}$ 233-235 °C); (KBr): ῡ= 3445, 3030, 1631, 1492, 1374, 1135, 1070 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 12.60 (s, 1H), 7.94 (d, *J* = 7.7Hz, 2H), 7.56-7.22 (m, 12H), 2.28 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ= 146.6, 138.8, 135.8, 131.4, 129.8, 128.5, 128.0, 127.5, 126.8, 125.2, 21.3 ppm; ESIMS: *m/z*: 311 (M^{+1}).

*4-(4,5-diphenyl-1H-imidazol-2-yl)phenol (**4c**):* White solid, m.p. 234-236 ^{o}C ($^{Lit.[81]}$ 232-233 ^{o}C); IR (KBr): ῡ= 3590, 3440, 3274, 3050, 1705, 1280 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 12.42 (s, 1H), 9.70 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.45-7.22 (m, 10H), 6.72 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ= 157.8, 146.3, 137.5, 135.7, 131.8, 129.3, 128.8, 128.2, 127.7, 127.1, 126.7, 120.5, 114.8 ppm . ESIMS: *m/z*: 313 (M^{+1}).

*2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole (**4d**)*: White solid, m.p. 226-228 °C ($^{Lit.[81]}$ 220-223 °C) IR (KBr): ῡ= 3420, 3055, 2965, 1610, 1496, 1485, 1250 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ =12.48 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.54-7.20 (m, 10H), 7.05 (d, *J* = 8.3 Hz, 2H), 3.86 (s, 3H)

ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ =159.5, 145.1, 129.4, 128.7, 128.3, 127.6, 127.5, 126.6, 126.3, 122.9, 113.7, 54.8 ppm. ESIMS: *m/z*: 327 (M^{+1}).

*2-(3,4-dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (**4e**)*: White solid, m.p. 222-224 °C (Lit.[94] 220-221 °C); IR (KBr): ῡ= 3445, 3048, 2965, 1640, 1552, 1482, 1240, 1047 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d6*): δ= 12.54 (brs, 1H), 7.62-7.56 (m, 3H), 7.54-7.44 (m, 4H), 7.36 -7.24 (m, 6H), 6.84 (d, 1H), 3.90 (s, 3H), 3.89 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-*d6*): *δ*=150.2; 148.6, 145.4, 129.7, 128.2, 127.5, 122.9, 117.9, 111.8, 109.2, 55.7, 55.5 ppm; ESIMS: *m/z*: 357(M^{+1}).

*4-(4,5-diphenyl-1H-imidazol-2-yl)-N,N-dimethylaniline (**4f**)*: White Solid, m.p. 256-258 °C (Lit.[81]256-259 °C); IR (KBr): ῡ= 3424, 2936, 2865, 1684, 1649, 1610, 1554, 1512, 1446, 1360 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ= ppm δ 12.88 (brs, 1H), 7.74 (d, 1H), 7.54-7.36 (m, 10H), 6.88 (d, 1H), 2.24 (s, 6H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ= 149.6, 145.1, 128.3, 127.6, 127.5, 126.8, 126.1, 117.9, 111.8, 41.6 ppm; ESIMS: m/z: 340 (M^{+1}).

*2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (**4g**)*: White solid, m.p. 260-262 °C (Lit.[81]262-264°C); IR (KBr): ῡ= 3420, 3061, 2955, 1662, 1610, 1495, 1440, 1010 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d6*): δ= 12.72 (1H, s,), 7.95 (2H, d,), 7. 52 (2H, d,), 7.40-7.16 (10H, m) ppm; ^{13}C NMR (75 MHz, DMSO-*d6*): δ= 144.3, 136.1, 133.3, 131.8, 129.7, 129.3, 128.0, 128.2, 127.8, 127.5, 126.4 ppm; ESIMS: m/z: 330 (M^+), 332 (M^{+2}).

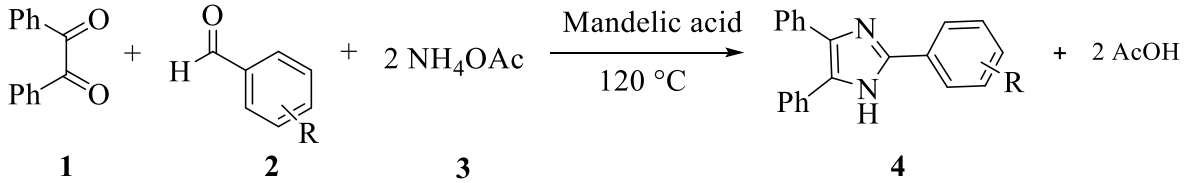
2-(4-bromophenyl)-4,5-diphenyl-1H-imidazole (***4h***): Reddish solid, m.p. 242-244 °C (Lit.[34] 244-246 °C); IR (KBr): ῡ= 3455, 3062, 2947, 1610, 1467, 1320, 1073 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d6*) δ= 12.76 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.74 (d, *J*= 7.9 Hz, 2H), 7.34-7.54 (m, 10H) ppm; ^{13}C NMR (75 MHz, DMSO- *d6*) δ= 144.3, 137.4, 135.7, 131.6, 129.8, 129.3, 128.5, 127.7, 127.1, 123.1 ppm; ESIMS: *m/z*: 374 (M^+), 376 (M^{+2}).

2-(4-Nitrophenyl)-4, 5-diphenyl-1H-imidazole (***4i***): Yellow solid, m.p. 222-224 °C (Lit.[34] 225 °C); IR (KBr): ῡ = 3425, 3081, 1610, 1586, 1523, 1377 cm^{-1}; ^{1}H NMR (300 MHz, DMSO- *d6*) δ= 12.61 (br, s, 1H); 7.26-8.48 (m, 14H) ppm. ^{13}C NMR (75 MHz, DMSO-*d6*) δ= 147.2, 143.4, 138.3, 136.1, 135.07, 131.6, 130.8, 129.3, 129.0, 128.3, 127.1, 126.4, 124.6 ppm; ESIMS: *m/z*: 342 (M^{+1}).

*2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole (**4j**)*: Yellow solid, m.p. 314-316 °C [Lit.[81] >300 °C]; IR (KBr): ῡ= 3430, 3086, 1605, 1524, 1362, 1075 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d6*) (ppm) δ= 12.74 (s, 1H), 8.90 (s, 1H), 8.48 (d, 1H, J = 7.8 Hz), 8.20 (d, 1H, J = 8.1Hz), 7.68 (t, 1H, J = 7.8Hz), 7.53-7.32 (m, 10H) ppm; ^{13}C NMR (75 MHz, DMSO-*d6*) δ= 150.1, 145.9, 133.1, 131.8, 130.8, 129.3, 128.2, 127.1, 123.1, 122.2 ppm; ESIMS: *m/z*: 342 (M^{+1}).

3. Results and Discussion

In a typical experimental procedure, the condensation reaction occurs in between equimolar amount of benzil (1) and aromatic aldehyde (2) with two moles of ammonium acetate (3) in presence of mandelic acid as organocatalyst at 120 °C. The reaction was completed within 30 minutes to obtain the corresponding, 2,4,5-trisubstituted Imidazoles (**4a**) derivative in excellent yields (Scheme 1).



1 **2** **3** **4**

Scheme 1. Synthesis of 2,4,5-trisubstituted Imidazoles (**4a**) derivative catalyzed by mandelic acid

For the optimization of catalyst and the reaction conditions, initially the reaction was carried out in absence of catalyst under solvent-free condition but desired product was not obtained even extending the reaction time. So the use of catalyst is essential for progress of reaction. By considering the importance of catalyst, we chose mild, inexpensive, nontoxic, highly stable and readily available mandelic acid as catalyst.

Table 1. Optimization of catalyst for synthesis of 2,4,5-triaryl imidazole (**4a**)

No	Mandelic acid (mol %)	Temperature (°C)	Time (min)	Isolated Yields (%)
1	No catalyst	rt	240	--
2	No catalyst	120	90	trace
3	5	120	30	30
4	10	120	30	55
6	15	120	30	70
7	**20**	**120**	**30**	**90**
8	25	120	30	88

rt= room temperature

Initially, the screening of catalyst was done by using different mole ratio from 5-25% under solvent-free conditions. The yield of product was not observed in absence of catalyst at room temperature. But by increasing the reaction temperature upto 120 ^{o}C, trace amount product was obtained. The yield of product progressively increases with increasing the amount of catalyst till 20% mole at 120 ^{o}C. Further increasing the amount of catalyst 25% mole, no significant improvment was observed in the reaction rate. Thus, the observation shows that 20% mole equivalent of mandelic acid is enough for the completion of reaction (Table 1). After optimization of catalyst, we moved towards screening of solvents effect using various solvents, like H_2O, EtOH, AcOEt, Acetone, DCM, CH_3CN and THF. The observation shows that solvent-free condition is best reaction condition in terms of the completion of reaction and yield of products other than those obtained in any of the solvents investigated (Table 2).

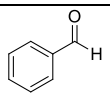
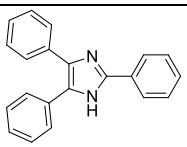
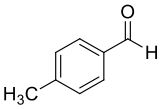
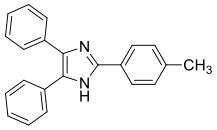
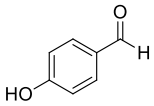
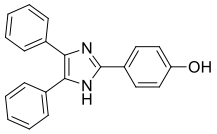
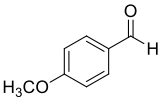
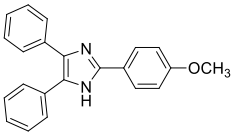
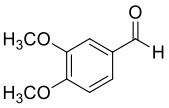
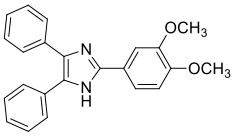
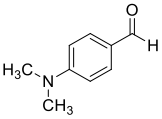
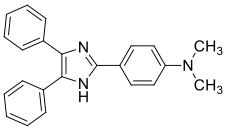
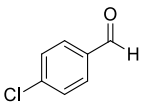
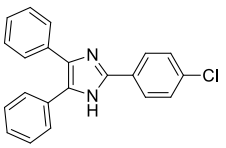
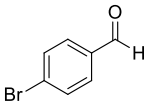
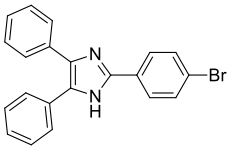
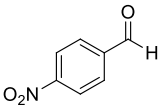
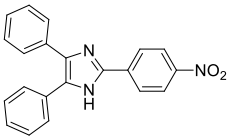
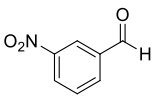
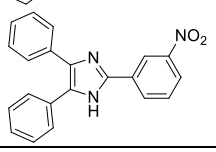
Table 2. Effect of solvent for mandelic acid catalyzed synthesis of 2,4,5-triaryl imidazole (**4a**)

No	Solvent	Temperature (^{o}C)	Time (min)	Isolated Yields (%)
1	H_2O	Reflux	60	trace
2	EtOH	Reflux	60	35
3	AcOEt	Reflux	60	38
4	Acetone	Reflux	60	40
5	DCM	Reflux	60	45
6	CH_3CN	Reflux	60	25
7	THF	Reflux	60	40
8	**Solvent-free**	**120**	**30**	**90**

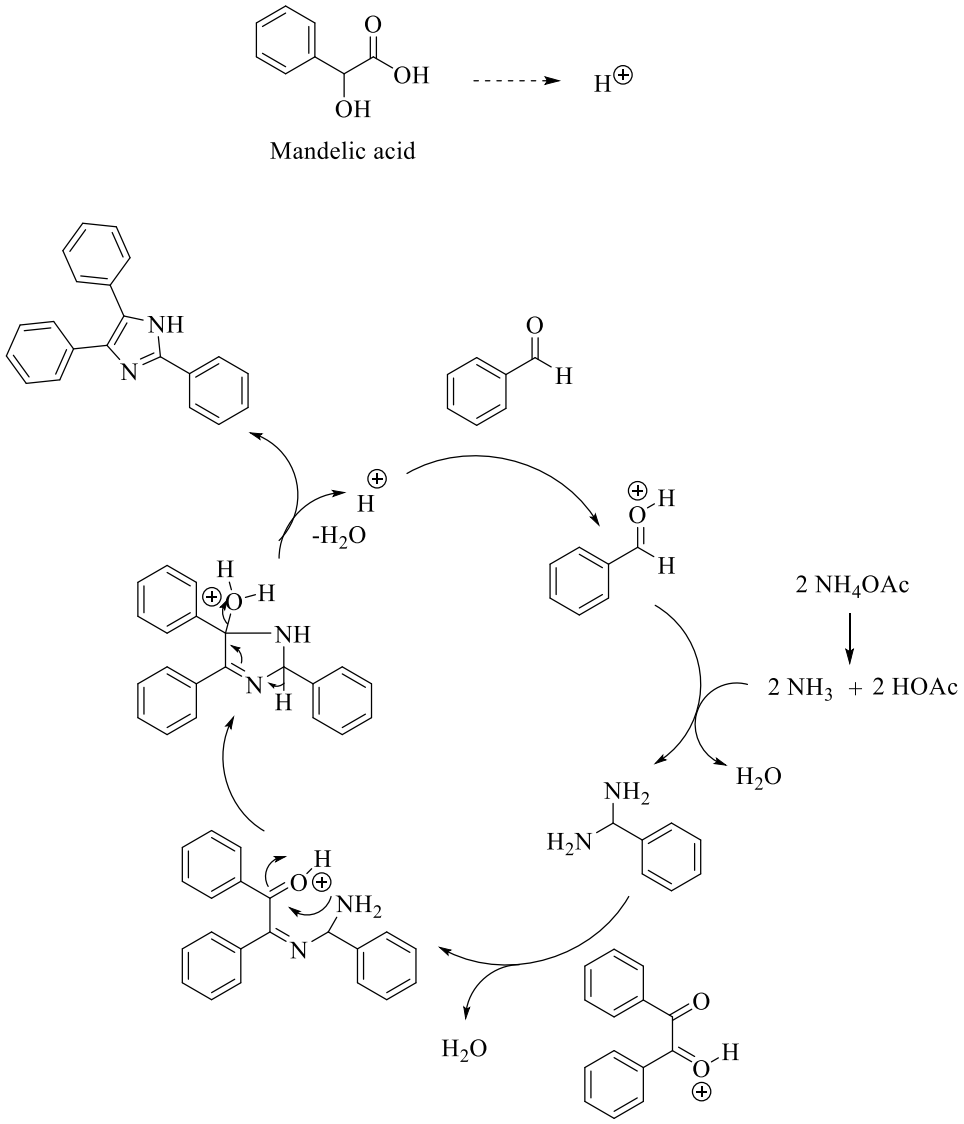
Based on the optimized reaction conditions, a variety of aryl aldehydes were reacted with benzil and ammonium acetate for the synthesis of 2,4,5-triaryl imidazole derivatives (**4a-4j**) to demonstrate the efficiency of this catalyst. This methodlogy works well for both aromatic aldehydes containing electron withdrawing as well as electron donating groups. The aromatic aldehyde having electron withdrawing group obtained in good yield while electron donating groups give somewhat reduced yield in appropriate reaction time. All the reactions were completed within 30 minutes of reaction time with excellent yields and the details were clearly mentioned in Table 3.

2,4,5-trisubstituted imidazoles

Table 3. Synthesis of the 2, 4, 5- trisubstituted imidazoles derivatives

No.	Aldehyde	Product	Reaction Time (min)	Yield[a] (%)	M.P. ºC [Lit. M.P.][Ref]
a			**30**	**90**	270-272 [267-269][81]
b			**30**	**88**	232-234 [233-235][81]
c			**30**	**87**	234-236 [232-233][81]
d			**30**	**83**	226-228 [220-223][81]
e			**30**	**80**	222–224 [220–221][94]
f			**30**	**85**	256-258 [256-259][81]
g			**30**	**90**	260-262 [262-264][81]
h			**30**	**90**	242-244 [244-246][34]
i			**30**	**91**	222–224 [225][94]
j			**30**	**89**	314-316 [>300][81]

[a]Isolated yields



Scheme 2. Plausible Reaction Mechanism

The formation of product can be explained as shown in plausible reaction mechanism[79] (Scheme-2). The acidic proton from mandelic acid has activated the carbonyl carbon group of aromatic aldehyde by making coordination with oxygen, which leads to formation of diamine with two moles of ammonia obtained from ammonium acetate. Then the condensation reaction occurs between diamine and pre-activated carbonyl carbons of diketone. After cyclisation followed by proton transfer occur to formed desired product.

4. Conclusion

In summary, we have demonstrated a simple, inexpensive and novel three-component methodology for the green synthesis of 2,4,5-trisubstituted imidazoles derivatives by using various aromatic aldehydes, benzil and ammonium acetate. The present method tenders noteworthy advantages such as economical, nontoxic, highly stable organo-catalyst, solvent-free conditions and

shorter reaction time with high conversions of product in excellent yield. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopy, and Mass spectrometry.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

Acknowledgements

The authors are grateful to department of chemistry, B. N. N. College, Bhiwandi and DST-FIST Delhi for providing laboratory and instrumentation facility.

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