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MICROWAVE-ASSISTED ONE-POT SYNTHESIS OF TRISUBSTITUTED IMIDAZOLES ON SOLID SUPPORT

Yu Xu, Li-Feng Wan, Hojatollah Salehi, Wei Deng, and Qing-Xiang Guo*

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China (e-mail: qxguo@ustc.edu.cn)

Abstract– A solvent–free microwave-assisted synthesis of trisubstituted imidazoles is reported. The imidazoles are produced by the condensation of α-hydroxyketone with an aldehyde over silica gel or alumina impregnated with ammonium acetate as the solid support in short time with good yields. An air oxidation mechanism is proposed, and this clean air oxidation considerably reduces the cost of imidazole synthesis.

INTRODUCTION

Recently, microwave-assisted method in organic synthesis is quickly growing.[1] Many organic reactions proceed much faster and get higher yields under microwave irradiation compared to conventional heating. In many cases reactions that normally require very long time at reflux temperatures under classical conditions can be completed within several minutes or even seconds in a microwave oven, even at comparable reaction temperatures.

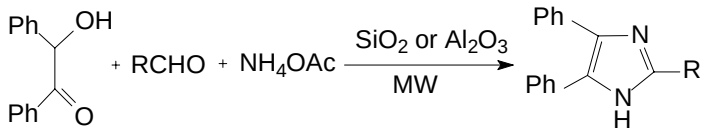
Compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes.[2] Numerous methods for the synthesis of highly substituted imidazoles were reported.[3-9] All these methods involve fussy treatment and yield relatively large amounts of waste.

Nevertheless, two research groups have recently reported a one-pot condensation of benzil, aldehyde, amine and ammonium acetate on alumina or silica solid support under microwave irradiation.[10, 11] The use of microwave irradiation considerably shortens the reaction time and circumvents harsh reaction conditions. The use of solid support in a solventless fashion greatly eases work-up procedures and reduces waste production.

The above reported method has recently been successfully used in our laboratory for the synthesis of some tetrasubstituted imidazole derivatives.[12] However, to our surprise we found that use of benzoin instead of benzil in the condensation could also yield the desired product efficiently. The benzils are

usually prepared from benzoins catalyzed by various toxic oxidants, [13] so direct use of benzoin rather than benzil in the synthesis of imidazoles represents a significant improvement in the syntheses toward to greener chemistry.

Therefore, in the present paper, we wish to report a microwave-assisted three-component condensation of benzoin, aldehyde and ammonium acetate on silica gel or alumina as an efficient and facile one-pot synthesis of trisubstituted imidazoles (Scheme 1).

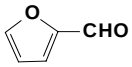


Scheme 1

RESULTS AND DISCUSSION

Trisubstituted imidazoles were synthesized under microwave irradiation in good yield (Table 1). In order to avoiding overheating, two 10-minute irradiations were performed. All products were characterized by IR, MS, and ^{1}H NMR spectra.

Table 1 Solvent-free synthesis of trisubstituted imidazoles under microwave irradiation

Entry	RCHO	Time (min) *	Yield (%)	
			SiO_2	Al_2O_3
a	PhCHO	10×2	70	67
b	*m*-$NO_2C_6H_4CHO$	10×2	74	61
c	*o*-ClC_6H_4CHO	10×2	76	68
d	*p*-$NMe_2C_6H_4CHO$	10×2	54	51
e	*p*-HOC_6H_4CHO	10×2	84	82
f	*o*-HOC_6H_4CHO	10×2	78	77
g	*p*-$MeOC_6H_4CHO$	10×2	92	86
h	$PhCH_2CHO$	10×2	53	50
i		10×2	65	48
j	Me_2CHCH_2CHO	10×2	50	45

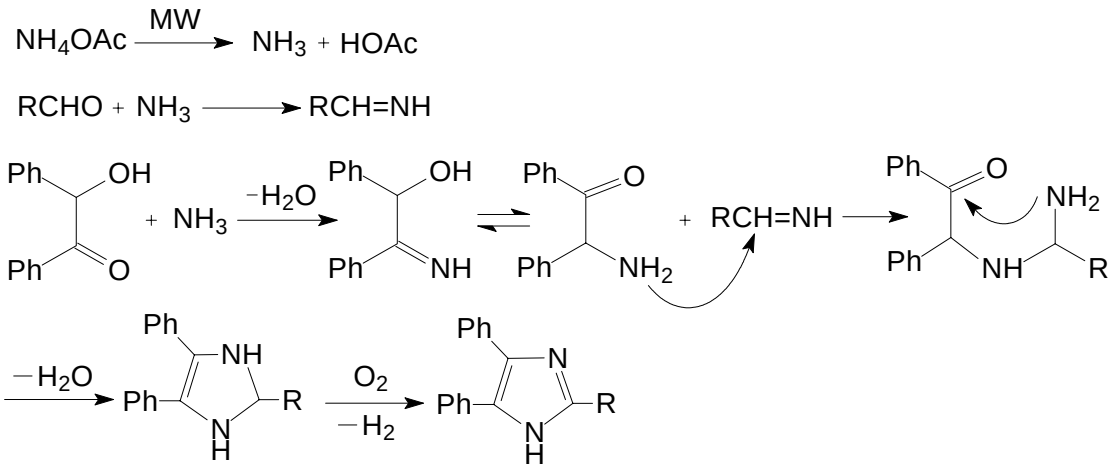
* Irradiation for two 10 min intervals with cooling to rt between intervals

From Table 1, it can be seen that this procedure could be applied to a broad range of aldehydes. The results indicated that good yields were obtained when the aromatic aldehydes were used as starting materials, however, when aliphatic aldehyde was used, the yield is not so good (Entries h, j), but still acceptable. And when there is electron-donating group on the aromatic rings, better yields can be obtained (Entries e, f, g). Comparing with alumina, silica gel was more efficient under the same conditions.

Interestingly, it was found that benzoin could be used in the condensation yielding imidazole in absence of any oxidizing reagent in our early research.[12] A control experiment of the condensation of benzoin, aldehyde and ammonium acetate under conventional acetic acid reflux conditions was run, no corresponding imidazole was isolated from the reaction mixture. It was in agreement with the previous finding that an oxidizing reagent such as Cu(II) was needed in the conventional condensation.[4]

And it was reported recently by Balalaie *et al.*[14] that benzoins were oxidized on zeolite A using microwave irradiation under solvent-free conditions. It was proposed that the zeolite A was significant in the Balalaie's benzoin oxidation. In our study the simple silica gel and alumina were adequate for a rapid and clean oxidation of the condensation mixture to imidazole. And at the same time a contrastive experiment of the condensation of benzoin, aldehyde and ammonium acetate over graphite was run, the target compound was obtained too. This finding demonstrated that air functioned as oxidant in the conversion.

It's very interesting that we get a by-product which is tetraphenylpyrazine in the reactions. It was found that the by-product was obtained by the two-component condensation of benzoin and ammonia acetate on silica gel under microwave irradiation. However, it was also found that the condensation of benzil and ammonia acetate can produce the other product, triphenyloxazole which is not found in the synthesis of trisubstituted imidazoles, on silica gel under microwave irradiation. In the classic approach, α-hydroxyketone was oxidized to form α-dione firstly and then α-dione, aldehydes, and ammonia acetate condensed to produce trisubstituted imidazoles according to the reference.[4] This finding demonstrated that benzoin is not oxidized before condensation. So the mechanism for this reaction under microwave irradiation is different from that in the conventional heating. The mechanism is proposed as Scheme 2.



Scheme 2

Based on the results described above, we can conclude that the microwave-assisted one-pot procedure on the surface of silica gel or alumina provides an efficient method for the synthesis of trisubstituted imidazoles by a simple three-component condensation under solvent-free conditions. An air oxidation

mechanism is proposed, and this clean air oxidation considerably reduces the cost of imidazole synthesis. And oxidation process takes place after condensation which is different from that in the conventional heating.

EXPERIMENTAL

All reported yields are isolated yields after column chromatography. IR spectra were run on a Bruker spectrophotometer and expressed in cm-1 (KBr). 1H-NMR spectra were recorded on FT-NMR Bruker AV-300 (300 MHz) in DMSO-d_6 with TMS as internal reference. MS spectra were run on a GCT-CA064 spectrograph. Elemental analysis was performed by the Elementar Vario EL-III. A domestic microwave oven (Galanz WD800B, 20% power, 160 W) was used in all experiments.

Typical procedure for the synthesis of trisubstituted imidazoles as follows: A mixture of silica gel (15.4 g) or alumina (17 g) and ammonium acetate (7.7 g) was ground fully in a mortar. A solution of benzoin (1.06 g, 5 mmol) and aldehyde (5 mmol) in 20 mL of methylene chloride in a 100 mL round-bottom flask was added to the mixture. The solvent was allowed to evaporate under reduced pressure and the dry residue was irradiated for 10×2 min in a domestic microwave oven at 160W at 120 °C in the open beaker. The mixture was cooled to rt and extracted with methylene chloride (3×60 mL). The combined washes were filtered and the solvent was evaporated by a rotary evaporator. The resulting solid residue was purified by column chromatography.

2,4,5-triphenylimidazole (**3a**) IR(KBr): 3040.2(υ N-H), 1602.1, 1504.3 1462.4(υ C=C), 766.2, 698.5 (δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.68(s, 1H, NH), 7.40-8.14(m, 15H, $3C_6H_5$); MS m/z: $(M+H)^+$ 297.1393 (Calcd 297.1392), Anal. Calcd for $C_{21}H_{16}N_2$: C 85.10, H 5.44, N 9.46. Found C 85.04, H 5.40, N 9.56.

2-(3-nitrophenyl)-4,5-diphenylimidazole (**3b**) IR(KBr): 3056.4(υ N-H), 1602.6, 1540.8, 1522.4, 1443.3 (υ C=C,C=N), 845.4, 767.2, 698.7(δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H:13.11(s, 1H, NH), 8.97(s, 1H, C_6H_4), 8.50(d, 1H, J=9 Hz, C_6H_4), 8.21(d, 1H, J=9 Hz, C_6H_4), 7.78(t, 1H, J=9 Hz, C_6H_4), 7.25-7.57 (m, 10H, $2C_6H_5$); MS m/z: M^+ 341.1171 (Calcd 341.1164); Anal. Calcd for $C_{21}H_{15}N_3O_2$: C 73.88, H 4.43, N 12.31. Found C 73.85, H 4.38, N 12.25.

2-(2-chlorophenyl)-4,5-diphenylimidazole (**3c**) IR(KBr): 3063.4(υ N-H), 1602.3, 1503.2, 1479.2, 1446.2 (υ C=C,C=N), 762.3, 734.3, 694.3(δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.64(s, 1H, NH), 7.29-7.80(m, 14H, $2C_6H_5$, C_6H_4); MS m/z: $(M+H)^+$ 331.1006 (Calcd 331.1002); Anal. Calcd for $C_{21}H_{15}N_2Cl$: C 76.34, H 4.58, N 8.49, Cl 10.59. Found C 74.38, H 4.52, N 8.43, Cl 10.67.

2-(4-dimethylaminophenyl)-4,5-diphenylimidazole (**3d**) IR(KBr): 3057.8(υ N-H), 2917.8, 2818.1(υ C-H), 1526.6, 1445.6(υ C=C), 806.8, 761.1, 696.9(δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.32(s,

1H, NH), 7.89(d, 2H, J=9 Hz, C_6H_4), 7.28-7.56(m, 10H, $2C_6H_5$), 6.78(d, 2H, J=9 Hz, C_6H_4), 2.96(s, 6H, NMe_2); MS m/z: $(M+H)^+$ 336.1510 (Calcd 336.1501), Anal. Calcd for $C_{23}H_{17}N_3$: C 82.35, H 5.11, N 12.54. Found C 82.20, H 5.22, N 12.58.

2-(4-hydroxyphenyl)-4,5-diphenylimidazole (**3e**) IR(KBr): 3062.7(υ N-H), 1496.5, 1463.3(υ C=C), 829.6, 764.7, 696.4(δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.40(s, 1H, NH), 9.69(s, 1H, OH), 7.88 (d, 2H, J=7.5 Hz, C_6H_4), 6.83(d, 2H, J=7.5 Hz, C_6H_4), 7.20-7.53 (m, 10H, $2C_6H_5$); MS m/z: $(M+H)^+$ 313.1345 (Calcd 313.1341); Anal. Calcd for $C_{21}H_{16}N_2O$: C 80.74, H 5.17, N 8.97. Found C 80.89, H 5.08, N 8.90.

2-(2-hydroxyphenyl)-4,5-diphenylimidazole (**3f**) IR(KBr): 3209.2(υ O-H), 3062.7(υ N-H), 1601.9, 1539.6, 1490.2, 1444.0(υ C=C), 764.2, 693.7(δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 13.04(s, 1H, NH), 12.95 (s, 1H, OH), 8.03(d, 2H, J=7.5 Hz, C_6H_4), 6.97(d, 2H, J=7.5 Hz, C_6H_4), 7.25-7.53(m, 10H, $2C_6H_5$); MS m/z: $(M+H)^+$ 313.1348 (Calcd 313.1341); Anal. Calcd for $C_{21}H_{16}N_2O$: C 80.74, H 5.17, N 8.97. Found C 80.90, H 5.10, N 8.91.

2-(4-methoxyphenyl)-4,5-diphenylimidazole **(3g)** IR(KBr): 3057.0(υ N-H), 2934.0, 2859.0(υ C-H), 1600.1, 1538.8.5, 1497.8.5, 1445.3(υ C=C, C=N), 828.1(δAr-H), 766.1, 694.2(δPh-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.52(s, 1H, NH), 8.03(d, 2H, J=9 Hz, C_6H_4), 7.24-7.51(m, 10H, $2C_6H_5$), 7.02(d, 2H, J=9 Hz, C_6H_4), 3.82(s, 3H, CH_3); MS m/z: $(M+H)^+$ 327.1490 (Calcd 327.1497); Anal. Calcd for $C_{22}H_{18}N_2O$: C 80.95, H 5.56, N 8.59. Found C 80.78, H 5.66, N 8.44.

2-benzyl-4,5-diphenylimidazole **(3h)** IR(KBr): 3052.6(υ N-H), 2924.8(υ C-H), 1600.1, 1443.2(υ C=C, C=N), 764.5, 695.7(δPh-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.24(s, 1H, NH), 7.28-7.88(m, 15H, $3C_6H_5$), 3.60(s, 2H, CH_2); MS m/z: $(M+H)^+$ 311.1540 (Calcd 311.1548); Anal. Calcd for $C_{22}H_{18}N_2$: C 85.12, H 5.85, N 9.03. Found C 85.26, H 5.80, N 8.94.

2-(2-furyl)-4,5-diphenylimidazole **(3i)** IR(KBr): 3057.4(υ N-H), 1602.6, 1501.6, 1445.9(υ C=C), 764.8, 696.6(δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.82(s, 1H, NH), 6.64-8.09(m, 13H, $2C_6H_5$, C_4H_3O); MS m/z: $(M+H)^+$ 287.1189 (Calcd 287.1184); Anal. Calcd for $C_{19}H_{14}N_2O$: C 79.69, H 4.93, N 9.79. Found C 79.51, H 4.87, N 9.95.

2-isobutyl-4,5-diphenylimidazole **(3j)** IR(KBr): 3441.7(υ N-H), 1603.6, 1536.4, 1499.9, 1444.5(υ C=C), 762.8, 698.0(δAr-H); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ_H: 12.07(s, 1H, NH), 7.32-7.42(m, 10H, $2C_6H_5$), 2.05(d, 2H, J=7.5 Hz, CH_2), 1.24(m, 1H, CH), 0.90(d, 6H, J=7.5 Hz, $2CH_3$); MS m/z: $(M+H)^+$ 276.1623 (Calcd 276.1626); Anal. Calcd for $C_{19}H_{20}N_2$: C 82.56, H 7.30, N 10.97. Found C 82.43, H 7.44, N 10.91.

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