Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1709–1711

TETRAHEDRON LETTERS

A novel one-pot synthesis of tetrasubstituted imidazoles under solvent-free conditions and microwave irradiation

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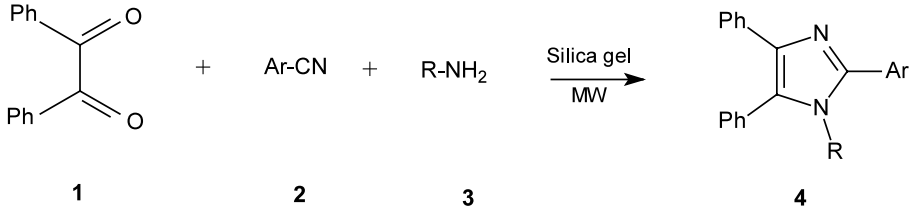
Received 15 October 2002; revised 1 November 2002; accepted 6 November 2002

Abstract—The one-pot, three-component condensation of benzil, benzonitrile derivatives and primary amines on the surface of silica gel under solvent-free conditions and microwave irradiation provided tetrasubstituted imidazoles in high yields.

The synthesis, reactions and biological properties of substituted imidazole constitutes a significant part of modern heterocyclic chemistry.[1] Compounds with the imidazole ring system have many pharmacological properties and play important roles in biochemical processes.[2] Many of substituted diaryl imidazoles are known as inhibitors of P38 MAP kinase.[3] There are several methods for the synthesis of highly substituted imidazoles.[1] The mostly used methods in the last decade are as follow: (a) synthesis via hetero-Cope rearrangement;[4] (b) four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin;[5] (c) reaction of *N*-(2-oxo)-amides with ammonium trifluoroacetate;[6] (d) reaction of *N*-alkyl-*N*-(β-keto)amides with ammonium acetate.[7]

Microwave-assisted rapid organic reactions constitute an emerging technology that make experimentally and industrially important organic syntheses more effective and more eco-friendly than conventional reactions.[8] In a continuation of our studies on microwave-assisted synthesis of heterocyclic compounds,[9] we developed a one-pot reaction catalyzed by silica gel and zeolite HY for the synthesis of trisubstituted[10] and tetrasubstituted imidazoles.[11] In the present work, we achieved a novel one-pot, three-component condensation of benzil, benzonitrile derivatives and primary amines on the surface of silica gel with acidic character under microwave irradiation as a new efficient method to produce 1,2,4,5-tetrasubstituted imidazoles (Scheme 1).

Limitations apply to the syntheses of highly substituted imidazole rings and generally these reactions cannot be carried out under neutral conditions.[12] In our first work[10] and another reported microwave method,[13] primary amines and ammonium acetate were used as nitrogen sources in imidazole rings. Now we use benzonitrile derivatives instead of ammonium acetate. The polarity of benzonitrile derivatives and primary amines makes them good candidates for reaction in a



1 2 3 4

Scheme 1.

Keywords: solvent-free organic synthesis; microwave irradiation; tetrasubstituted imidazoles.

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0040-4039/03/$ - see front matter
PII: S0040-4039(03)00018-2

microwave oven. Silica gel is used as a solid support in all of the experiments. Reaction of benzonitrile, benzil and benzylamine on the surface of silica gel under microwave irradiation produces **4a**. IR and ^{1}H NMR spectra of the product clearly indicated the formation of tetrasubstituted imidazole **4a**. The same reactions were carried out using benzil, benzonitrile derivatives and primary amines under the same conditions. The results are summarized in Table 1.

The structures of compounds **4a**–**h** were deduced from their elemental analyses, ^{1}H NMR and IR spectral data and melting points. The three-component condensation of benzil, benzonitrile and benzylamine was also performed in the absence of silica gel under neat conditions and microwave irradiation; however, the yield of **4a** was low (10%). A further problem encountered with these conditions is that the reactants and products adhered to the reaction vessel and led to irreproducible results. The temperature of the reaction mixture was 90°C at the end of irradiation under solvent-free conditions. Carrying out the condensation in refluxing toluene for 29 h resulted in **4a** with an 82% yield. Although we have not experimentally established the mechanism of formation of products, it seems that the existence of silica gel as acidic support under microwave irradiation can accelerate this new cyclocondensation reaction by increasing the reactivity of benzonitrile derivatives and benzil, and also by supporting the formation of polar intermediates.[14]

In conclusion, the one-pot nature of the present procedure makes it an acceptable alternative to multi-step approaches. It also simplifies the laborious procedures and offers considerable advantages, such as: elimination of solvents, the use of substances without any modification or activation, high yields, short reaction times, employment of reusable solid catalysts and environmentally friendly character over the existing methodologies.

*General procedure for the synthesis of tetrasubstituted imidazoles (**4a**–**h**)*:[15]

Benzil (421 mg, 2 mmol), benzonitrile derivatives (2–3 mmol), primary amine (3–5 mmol) and 2 g of silica gel were mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 8 min (optimized time) at 850 W. The progress of reaction was monitored by TLC using CH_2Cl_2–petroleum ether as eluent. The mixture was extracted with chloroform, and the solvent was removed by rotary evaporation. Further purification by column chromatography and recrystallization gave the desired products.

Table 1. Solvent-free synthesis of tetrasubstituted imidazoles under microwave irradiation

	Ar	R	Yield (%)[a]
a	Ph	$PhCH_2$	87
b	Ph	$PhCH(CH_3)$	92
c	4-$CH_3C_6H_4$	CH_3	78
d	4-$CH_3C_6H_4$	C_2H_5	87
e	4-$CH_3C_6H_4$	*iso*-C_4H_9	90
f	4-$CH_3C_6H_4$	$PhCH_2$	90
g	3-BrC_6H_4	$PhCH_2$	65
h	3-$NH_2C_6H_4$	$PhCH_2$	58

[a] In all experiments, the optimized time of irradiation was 8 min.

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15. *Selected data*:
1-Benzyl-2,4,5-triphenyl imidazole (**4a**): mp 160–161°C (ethanol, lit.[16] 163–164°C); IR (KBr): 2985, 1600, 1580, 1480 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.15 (s, 2H, CH_2), 6.70–7.80 (m, 20H, Ph).
1-(2-Phenylethyl)-2,4,5-triphenyl imidazole (**4b**): mp 98–100°C (ethanol); ^1H NMR ($CDCl_3$): δ 1.40 (d, 3H, $J=6.7$ Hz, CH_3), 4.60 (q, 1H, $J=6.7$ Hz, CH), 7.10–7.90 (m, 20H, Ph). Anal. calcd for $C_{29}H_{24}N_2$ (400.495): C, 86.97; H, 6.03; N 6.99. Found: C, 86.81; H, 6.14; N 6.91%.
1-Methyl-2-(4-methylphenyl)-4,5-diphenyl imidazole (**4c**): mp 209–210°C (*n*-hexane, lit.[16] 209–217°C); ^1H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 7.30–7.85 (m, 14H, Ar); IR (KBr): 2985, 1600, 1580, 1480 cm^{-1}.
1-Ethyl-2-(4-methylphenyl)-4,5-diphenyl imidazole (**4d**): mp 123–125°C (ethanol, water); IR (KBr): 2980, 1600, 1585, 1480 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H, $J=7.1$ Hz, CH_3), 2.35 (s, 3H, CH_3), 3.85 (q, 2H, $J=7.1$ Hz, CH_2), 7.05–7.85 (m, 14H, Ar).
1-Isobutyl-2-(4-methylphenyl)-4,5-diphenyl imidazole (**4e**): mp 150–152°C (ethanol); IR (KBr): 2950, 1600, 1580, 1480 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.3 (d, 6H, $J=6.6$ Hz, $2CH_3$), 1.00–1.40 (m, 1H, CH), 2.20 (s, 3H, CH_3), 3.60 (d, 2H, $J=7.5$ Hz, CH_2), 6.90–7.50 (m, 14H, Ar).
1-Benzyl-2-(4-methylphenyl)-4,5-diphenyl imidazole (**4f**): mp 165–166°C (ethanol, lit.[17] 162°C); IR (KBr): 2925, 1600, 1575, 1495, 1485 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.00 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 6.65–7.60 (m, 19H, Ar).
1-Benzyl-2-(3-bromophenyl)-4,5-diphenyl imidazole (**4g**): mp 157–160°C (ethanol); IR (KBr): 2925, 1610, 1600, 1575 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.04 (s, 2H, CH_2), 6.65–7.70 (m, 19H, Ar). Anal. calcd for $C_{28}H_{21}BrN_2$ (465.368): C, 72.26; H, 4.54; N, 6.02. Found: C, 72.44; H, 4.44; N, 6.14%.
1-Benzyl-2-(3-aminophenyl)-4,5-diphenyl imidazole (**4h**): mp 159–161°C (ether); IR (KBr): 3490, 3450, 1610, 1590, 1300 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.00 (s, 2H, CH_2), 6.60–7.70 (m, 19H, Ar). Anal. calcd for $C_{28}H_{23}N_3$ (401.485): C, 83.76; H, 5.76; N, 10.46. Found: C, 83.79; H, 5.73; N, 10.31%.
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