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ORIGINAL ARTICLE

Synthesis of 2,4,5-triarylated imidazoles via three-component domino reaction under catalyst-free conditions

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Abstract A one-pot synthesis of 2,4,5-triarylated imidazoles via three-component domino reaction of 2,2-dibromo-1,2-diarylethanones, ammonium acetate, and aryl aldehydes under catalyst-free conditions is developed. The scope of this reaction is studied. A possible mechanism is proposed based on experimental results.

1. Introduction

Imidazole is a class of very important heterocyclic compounds, which can be found in many natural products [1]. They are recognized to exhibit a large variety of important biological and pharmacological activities [2]. It has been reported that some imidazole derivatives can be used as herbicides [3], fungicides [3b,4], growth regulators [5], potent angiotensin II receptor antagonist [6], glucagon receptor antagonist [7], and inhibitors of interleukin (IL)-1 and 5-lipoxygenase [8]. Thus, the development of novel synthetic strategies of imidazole units is an interesting topic in modern organic chemistry. Among the numerous achievements [9,10], the one-pot synthesis of 2,4,5-triarylated imidazoles via three-component domino reaction of benzils, ammonium acetate, and aryl aldehydes is a very important protocol [9] (Fig. 1). This transformation has a rich history, since it was firstly reported by Cook and Jones in 1941 [9a]. Based on this reaction, various methods have been developed starting from benzils [9b–i]. However, to the best of our knowledge, the preparation of 2,4,5-triarylated imidazoles directly from 2,2-dibromo-1,2-diarylethanones has not been reported yet. Herein, we wish to report our recent

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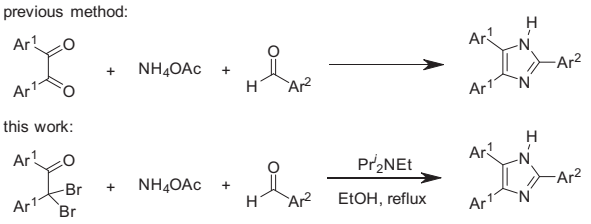

Figure 1 Methods applied for the synthesis of 2,4,5-triarylated imidazoles.

observations on the one-pot synthesis of 2,4,5-triarylated imidazoles via three-component domino reaction of 2,2-dibromo-1,2-diarylethanones, ammonium acetate, and aryl aldehydes under catalyst-free [11] conditions (Fig. 1).

2. Methods

2.1. General experimental methods

^{1}H (400 MHz), ^{13}C (100 MHz), and ^{19}F (376 MHz) NMR spectra of samples in DMSO-d_6 (unless stated otherwise) were recorded on an AVANCE III 400 spectrometer. IR spectra were recorded on an Avatar 360 FT-IR spectrometer. HRMS (ESI) determinations were carried out on a Bruker Daltonics MicrOTOF II spectrometer. Melting points were determined on a WRS-2 apparatus.

2.2. Typical procedure for synthesis of 2,2-dibromo-1,2-diarylethanones

Thionyl bromide was added to a solution of 1,2-diarylethanone in anhydrous benzene. The resulting reaction mixture was refluxed and then cooled to room temperature, quenched by saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$. Filtration, concentration, and purification by flash chromatography on silica gel afforded 2,2-dibromo-1,2-diarylethanones.

*2.2.1. 2,2-Dibromo-1,2-bis(4-methoxyphenyl)ethanone (**1b**)*

Yield (81%); mp 127.7–128.5 °C (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 9.2 Hz, 2H, Ar–H), 7.56 (d, J = 9.2 Hz, 2H, Ar–H), 6.86 (d, J = 9.2 Hz, 2H, Ar–H), 6.75 (d, J = 9.2 Hz, 2H, Ar–H), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9 (C═O), 163.3 (Ar–C), 160.2 (Ar–C), 134.0 (Ar–C), 133.7 (Ar–C), 128.2 (Ar–C), 123.0 (Ar–C), 114.0 (Ar–C), 113.3 (Ar–C), 69.9 (CBr_2), 55.4 (OCH_3); IR (neat) 1682, 1597, 1570, 1507, 1458, 1440, 1420 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}Br_2NO_3$ ($M + NH_4^+$) 429.9648, found 429.9654.

*2.2.2. 2,2-Dibromo-1-(4-fluorophenyl)-2-phenylethanone (**1c**)*

Yield (27%); mp 88.4–90.9 °C (ethyl acetate/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 2H, Ar–H), 7.63 (d, J = 7.2 Hz, 2H, Ar–H), 7.43–7.30 (m, 3H, Ar–H), 6.94 (t, J = 8.8 Hz, 2H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7 (C═O), 165.3 (d, J = 260 Hz, C–F), 140.8 (Ar–C), 134.3 (d, J = 9.5 Hz, Ar–C), 129.8 (Ar–C), 129.0 (Ar–C), 126.8 (d, J = 3.6 Hz, Ar–C), 126.6 (Ar–C), 115.3 (d, J = 20 Hz, Ar–C), 69.0 (CBr_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.7; IR (neat) 1694, 1594, 1505, 1446, 1407 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_9Br_2NaFO$ ($M + Na^+$) 392.8896, found 392.8877.

*2.2.3. 2,2-Dibromo-2-(4-fluorophenyl)-1-phenylethanone (**1d**)*

Yield (28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H, Ar–H), 7.68–7.60 (m, 2H, Ar–H), 7.45 (t, J = 7.2 Hz, 1H, Ar–H), 7.32–7.22 (m, 2H, Ar–H), 7.05 (t, J = 8.6 Hz, 2H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9 (C═O), 162.8 (d, J = 250.9 Hz, C–F), 137.0 (d, J = 3.6 Hz, Ar–C), 133.3 (Ar–C), 131.4 (Ar–C), 130.5 (Ar–C), 128.9 (d, J = 8.7 Hz, Ar–C), 128.1 (Ar–C), 115.9 (d, J = 21.9 Hz, Ar–C), 68.1 (CBr_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.5; IR (neat) 1699, 1601, 1507, 1449, 1409 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_9Br_2NaFO$ ($M + Na^+$) 392.8896, found 392.8881.

*2.3. Typical Procedure for synthesis of 2,4,5-triarylated imidazoles (**3aa-3bi, 12, and 13**)*

The reaction of 2,2-dibromo-1,2-diarylethanone, ammonium acetate, aryl aldehyde, and Pr^i_2NEt in EtOH was carried out at refluxing temperature under argon atmosphere. When the reaction was completed as monitored by TLC, the solvent was removed and the residue was purified by flash column chromatography on silica gel to afford 2,4,5-triarylated imidazole.

*2.3.1. 4,5-Diphenyl-2-(o-tolyl)-1H-imidazole (**3aa**) [9h]*

Yield (58%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (brs, 1H, NH), 7.74–7.68 (m, 1H, Ar–H), 7.58–7.16 (m, 13H, Ar–H), 2.64 (s, 3H, CH_3).

*2.3.2. 2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (**3ab**) [9b]*

Yield (52%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (brs, 1H, NH), 8.01 (d, J = 8.4 Hz, 2H, Ar–H), 7.55–7.18 (m, 10 H, Ar–H), 7.04 (d, J = 8.4 Hz, 2H, Ar–H), 3.82 (s, 3H, OCH_3).

*2.3.3. 2-(3-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (**3ac**) [12]*

Yield (51%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (brs, 1H, NH), 7.72–7.64 (m, 2H, Ar–H), 7.60–7.18 (m, 11H, Ar–H), 6.95 (d, J = 8.0 Hz, 1H, Ar–H), 3.84 (s, 3H, OCH_3).

*2.3.4. 2-(2-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (**3ad**) [9g]*

Yield (50%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (brs, 1H, NH), 8.04 (d, J = 7.6 Hz, 1H, Ar–H), 7.55–7.03 (m, 13H, Ar–H), 3.92 (s, 3H, OCH_3).

*2.3.5. 4,5-Diphenyl-2-(p-tolyl)-1H-imidazole (**3ae**) [9b]*

Yield (53%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (brs, 1H, NH), 7.97 (d, J = 8.4 Hz, 2H, Ar–H), 7.57–7.18 (m, 12H, Ar–H), 2.35 (s, 3H, CH_3).

*2.3.6. 4,5-Diphenyl-2-(m-tolyl)-1H-imidazole (**3af**) [9b]*

Yield (55%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (brs, 1H, NH), 7.93 (s, 1H, Ar–H), 7.87 (d, J = 8.0 Hz, 1H, Ar–H), 7.58–7.15 (m, 12H, Ar–H), 2.39 (s, 3H, CH_3).