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ORIGINAL PAPER

Synthesis of 2,3,4,5-tetrasubstituted pyrroles and 1,4-dihydro-tetraarylpyrazines using acidic alumina as a heterogeneous catalyst

Khodabakhsh Niknam[1] · Hashem Sharghi[2] · Mohsen Khataminejad[1]

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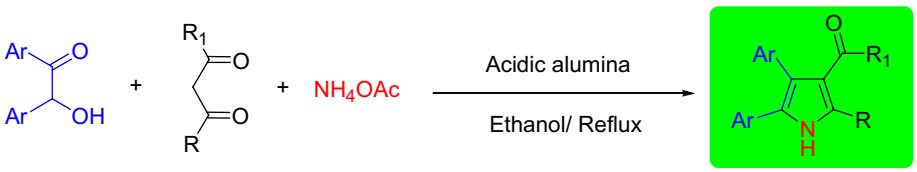
Abstract Some new 2,3,4,5-tetrasubstituted pyrroles were synthesized via three-component condensation reaction of benzoin derivatives, 1,3-dicarbonyl compounds, and ammonium acetate using acidic Al_2O_3 as an efficient and reusable heterogeneous catalyst in refluxing ethanol in high yields. Also, acidic alumina was catalyzed 1,4-dihydro-tetraarylpyrazines by the condensation reaction of benzoins and ammonium acetate in refluxing ethanol in high yields. Alumina showed much the same efficiency when used in consecutive reaction runs.

Graphical Abstract Acidic alumina was used as heterogeneous acidic catalyst for the synthesis of tetrasubstituted pyrroles in refluxing ethanol. The catalyst could be recycled for several times.



Ar = C_6H_5-, 4-Me-C_6H_4-, 4-F-C_6H_4-, 4-Cl-C_6H_4-

Keywords Acidic alumina · Pyrroles · 1 · 4-Dihydro-tetraarylpyrazines · Synthesis · Heterogeneous catalyst

✉ Khodabakhsh Niknam
niknam@pgu.ac.ir

[1] Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran

[2] Chemistry Department, College of Science, Shiraz University, Shiraz 71454, Iran

Introduction

Pyrroles are prominent in pharmaceuticals and represent an important class of heterocyclic compounds [1–4]. They are commonly found as structural motifs in natural (storniamide A, halitulin, oroidin, lamellarin P, sceptrin, marinopyrrole B, and atorvastatin) and synthetic products [4, 5] (Fig. 1). Polyfunctionalized pyrroles have attracted particular attention in drug discovery due to their various pharmacological properties [4] such as antibacterials [6], antitumorals, as well as antifungal [7], anti-inflammatory [8], antioxidant [9], and central nervous system agents [4].

A variety of classical methods have been reported for the synthesis of pyrroles, such as the Barton–Zard [10], Hantzsch [11], Knorr [12, 13], Trofimov [14], Paal–Knorr [15, 16], and Clauson–Kaas [17–19] reactions and their modifications. In addition, pyrroles have also been synthesized by the Huisgen reaction [20–22], cyclization of *N*-propargylic derivatives [23, 24], including propargyl aziridines [25, 26], through the cyclocondensation of vinyl azides with 1,3-dicarbonyls [27, 28], transition-metal-catalyzed cyclization [29], [3 + 2] cycloadditions [30], and multi-component reactions [4, 31–39], among various other alternatives. Nevertheless, some of these methods need multiple steps, expensive or prefunctionalized substrates, and using reagents which generate halide wastes. With

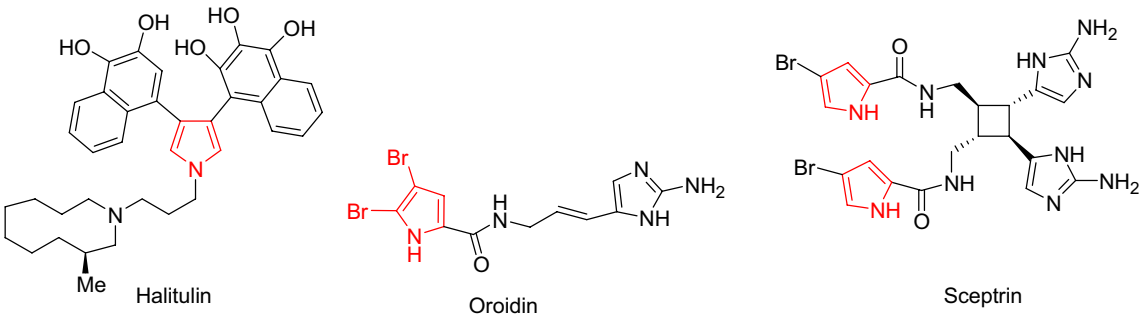


Fig. 1 Some polysubstituted pyrrole-containing bioactive natural product

respect to green chemistry, the development of methods with starting from inexpensive and easily available substrates remains a demanding goal.

Alumina, silica gel, zeolites, and clays are the most important class of solids which have been used for surface organic chemistry [40–47]. Among them, acidic alumina that commonly used for column chromatography certainly has one of the most interesting of these surface properties, which suggests a very rich organic chemistry may occur there.

We report here the synthesis of 2,3,4,5-tetrasubstituted pyrroles via three-component condensation reaction of benzoins, 1,3-dicarbonyl compounds, and ammonium acetate using acidic alumina as catalyst in refluxing ethanol.

Experimental

Chemicals and reagents

Chemicals were purchased from Merck and Aldrich chemical companies. The products were characterized by comparison of their spectral and physical data with those reported in the literature. For the recorded ^{1}H-NMR spectra, we used Bruker Ultrashield (400 MHz) in pure deuterated $CDCl_3$ or DMSO-d_6 solvent with tetramethylsilane (TMS) as internal standards. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at 70 eV. FTIR spectroscopy (Shimadzu FTIR-8300 spectrophotometer) was employed for characterization of the products. Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel PolyGram SIL G/UV254 plates. Column chromatography was carried out on columns of silica gel 60 (70–230 mesh). Acidic alumina was purchased from Merck (Aluminum oxide 90 active acidic (0.063–0.2 mm).

General procedure for the synthesis of 2,3,4,5-tetrasubstituted pyrroles

To a mixture of benzoin derivative (1 mmol), 1,3-dicarbonyl compound (1 mmol) and NH_4OAc (1.5 mmol) in ethanol (3 mL) were added acidic alumina (0.04 g, 0.04 mol %), and the mixture was refluxed for appropriative times (Table 2). After completion of the reaction (as indicated by thin-layer chromatography), warm ethanol (3 × 5 mL) was added and the catalyst was separated by filtration. The filtrated was cooled to room temperature and precipitated was filtered. For further purification, the precipitates were recrystallized from ethanol to give corresponding product. The products **1d**, **1i**, **1j**, and **1 k** were purified by silica gel column chromatography employing *n*-hexane/ethyl acetate as the eluent.

1-(2-Methyl-4,5-di-*p*-tolyl-1H-pyrrole-3-yl)-ethanone (1a) (Table 2, entry 1)

White solid, recrystallized from ethanol, mp 237–238 °C (Lit. [34] 237–238). IR (KBr): 3286.5 (N–H), 1604.7 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 1.74 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.99–7.05 (m, 4H, Ar), 7.09 (d, 2H, $J = 7.6$ Hz, Ar), 7.17 (d, 2H, $J = 8.0$ Hz, Ar), 11.52 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 20.6, 20.8, 30.5, 121.5, 122.0, 126.4, 126.5, 128.7, 128.9, 129.4, 130.6, 134.0, 134.8, 135.3, 135.7, 194.5.

2-Methyl-4,5-di-*p*-tolyl-1H-pyrrole-3-carboxylic acid methyl ester (1b) (Table 2, entry 2)

White solid, recrystallized from ethanol, 90 % yield; mp 175–176 °C. IR (KBr): 3317.3 (N–H), 1681.8 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.21 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 6.97–7.07 (m, 8H, Ar), 11.47 (s, 1H, NH). ^{13}C NMR (100 MHz; $CDCl_3$) δ (ppm): 13.3, 20.6, 20.8,

50.0, 111.0, 121.9, 126.7, 127.1, 128.1, 128.7, 129.4, 130.4, 133.3, 134.8, 135.3, 135.3, 165.1. MS (EI, 70 eV): *m/z* (%): 320 ($M^+ + 1$, 22.6), 319 (M^+, 45.9), 244 (17.4), 149 (52.2), 83 (base peak). Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39; found: C, 78.74; H, 6.67, N, 4.21.

2-Methyl-4,5-di-*p*-tolyl-1*H*-pyrrole-3-carboxylic acid benzyl ester (1c) (Table 2, entry 3)

White solid; recrystalized from ethanol, 89 % yield; mp 171–172 °C. IR (KBr): 3309.6 (N–H), 1678.1 (cm^{-1}) (N–C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.18 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 5.01 (s, 2H, OCH_2), 6.91–6.97 (m, 8H, Ar), 7.03–7.06 (m, 2H, Ar), 7.12–7.17 (m, 3H, Ar), 8.31 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.0, 20.1, 20.3, 64.2, 111.1, 121.8, 125.6, 126.4, 126.4, 126.7, 127.9, 128.1, 128.3, 128.7, 129.5, 132.0, 134.6, 134.7, 135.2, 135.4, 164.5. MS (EI, 70 eV): *m/z* (%) = 396 ($M^+ + 1$, 12.1), 395 (M^+, 38.1), 305 (18.1), 304 (base peak), 262 (5.1), 244 (5.2), 91 (11.5). Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54; found: C, 81.76; H, 6.39; N, 3.36.

1-(2-Methyl-4,5-di-*p*-tolyl-1*H*-pyrrole-3-yl)-phenyl-methanone (1d) (Table 2, entry 4)

Yellow solid, purified by column chromatography on silica gel, mp 220–221 °C. IR (KBr): 3309.6 (N–H), 1620.1 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.16 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 6.82–7.52 (m, 13H, Ar), 11.53 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 12.7, 20.6, 120.9, 121.5, 126.8, 127.0, 127.8, 128.2, 128.8, 129.4, 130.0, 131.3, 132.6, 133.4, 134.4, 135.5, 139.8, 192.8. MS: *m/z* (%):366 ($M^+ + 1$, 10.8), 365 (M^+, 34.8), 279 (17.4), 167 (30.4), 149 (base peak), 57 (80.7). Anal. Calcd for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83; found: C, 85.18; H, 6.38; N, 3.61.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-yl)-ethanone (1e) (Table 2, entry 5)

White solid, recrystallized from ethanol, mp 168–170 °C (Lit. [32] 170–172 °C). IR (KBr): 3197.0 (N–H), 1622.0 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.92 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.10–7.34 (m, 10H, Ar), 8.51 (s, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 15.2, 31.8, 123.5, 123.5, 127.1, 127.8, 128.0, 128.2, 129.1, 129.3, 131.9, 133.5, 137.0, 138.1, 197.6.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-carboxylic acid ethyl ester (1f) (Table 2, entry 6)

White solid, recrystallized from ethanol, mp 203–204 °C (Lit. [34] 206–208). IR (KBr): 3320.5 (N–H), 1682.0 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.93 (t, 3H, J = 7.1 Hz, CH_3), 2.51 (s, 3H, CH_3), 3.97 (q, 2H, J = 7.1 Hz, OCH_2), 7.00–7.21 (m, 10H, Ar), 8.26 (s, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 12.8, 12.9, 58.2, 111.6, 122.4, 125.3, 125.5, 125.7, 126.2, 126.6, 127.5, 129.7, 131.1, 134.4, 135.0, 164.6.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-carboxylic acid methyl ester (1g) (Table 2, entry 7)

White solid, recrystallized from ethanol, mp 183–184 °C (Lit. [34] 178–180). IR (KBr): 3313.1(N–H), 1680.0 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 2.62 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 7.11–7.26 (m, 10H, Ar), 8.29 (s, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 15.1, 51.7, 113.3, 124.5, 127.5, 127.7, 128.1, 128.8, 129.6, 131.9, 132.2, 133.3, 136.9, 137.1, 167.1.

2-Methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylic acid benzyl ester (1h) (Table 2, entry 8)

White solid; recrystalized from ethanol, 89 % yield; mp 204–205 °C. IR (KBr): 3309.0 (N–H), 1679.0 (cm^{-1}) (N–C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.50 (s, 3H, CH_3), 5.00 (s, 2H, OCH_2), 6.91–6.93 (m, 2H, Ar), 6.98–7.00 (m, 2H, Ar), 7.04–7.09 (m, 3H, Ar), 7.11–7.16 (m, 8H, Ar), 8.31 (s, 1H, NH). ^{13}C NMR (100 MHz; $CDCl_3$) δ (ppm): 13.0, 64.2, 111.2, 122.3, 125.4, 125.5, 125.7, 126.4, 126.5, 126.7, 126.7, 127.2, 127.4, 129.8, 131.1, 134.9, 135.0, 135.3, 164.4. MS (EI, 70 eV): *m/z* (%) = 369 ($M^+ + 2$, 3.3), 368 ($M^+ + 1$, 20.0), 367 (M^+, base peak), 366 (17.5), 338 (8.3), 322 (10.1), 265 (17.5), 105 (11.6), 77 (5.1). Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81; found: C, 81.47; H, 5.81; N, 3.52.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-yl)-phenyl-methanone (1i) (Table 2, entry 9).

Yellow solid, purified by column chromatography on silica gel, mp 218–219 °C (Lit. [34] 223–225). IR (KBr): 3286.5 (N–H), 1604.7 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 2.26 (s, 3 H, CH_3), 6.95–7.37 (m, 15 H, Ar), 11.65 (s, 1 H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ (ppm) 12.7, 121.0, 122.0, 125.7, 126.3, 126.8, 127.1, 127.6, 127.8, 128.9, 129.6, 130.2, 131.3, 132.2, 134.0, 135.6, 139.7, 192.8.

1-[4,5-Bis(4-fluorophenyl)-2-methyl-1*H*-pyrrol-3yl]-ethanone (1j) (Table 2, entry 10).

Yellow solid, purified by column chromatography on silica gel, 90 % yield; mp 239–240. IR (KBr): 3326.0 (N–H), 1621.0 (cm^{-1}) (N–C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.81 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.08–7.24 (m, 8H, Ar), 11.67 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.8, 30.5, 115.0, 115.3, 120.8, 121.9, 126.0, 128.6, 128.7, 132.6, 132.6, 135.2, 194.1. MS (EI, 70 eV): *m/z* (%) = 313 ($M^+ + 2$, 2.7), 312 ($M^+ + 1$, 26.4), 311 (M^+, 93.6), 310 (15.5), 297 (35.5), 296 (base peak), 281 (15.5), 266 (17.3), 253 (29.1), 95 (5.5). Anal. Calcd for $C_{19}H_{15}F_2NO$: C, 73.30; H, 4.86; F, 12.20; N, 4.50; found: C, 73.06; H, 4.88; N, 4.32.

1-[4,5-Bis-(4-fluoro-phenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid methyl ester (1k) (Table 2, entry 11)

Yellow solid, purified by column chromatography on silica gel, mp 211–213 °C (Lit. [38] 215–218). IR (KBr): 3287.0 (N–H), 1678.0 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.49 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 7.08–7.15 (m, 8H, Ar), 11.64 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 13.3, 50.1, 114.3, 115.0, 115.3, 115.5, 115.5, 127.2, 127.3, 128.8, 128.9, 132.2 ($^1J_{C-F}$ = 120.0 Hz), 132.4, 135.8, 164.9. MS: *m/z* (%): 329 ($M^+ + 2$, 3.6), 328 ($M^+ + 1$, 35.5), 327 (M^+, base peak), 312 (55.5), 296 (49.1), 266 (69.1), 253 (16.3), 95 (5.5).

1-[4,5-Bis-(4-chloro-phenyl)-2-methyl-1H-pyrrole-3-yl]-ethanone (1l) (Table 2, entry 12).

White solid, recrystallized from ethanol, mp 230–232 °C (Lit. [32] 234–235 °C). IR (KBr): 3318.0 (N–H), 1619.0 (cm^{-1}) (N–C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.90 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.99–7.01 (m, 2H, Ar), 7.17–7.19 (m, 4H, Ar), 7.31–7.33 (m, 2H, Ar), 8.55 (s, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.8, 31.4, 122.2, 128.4, 129.2, 129.3, 130.6, 132.5, 133.1, 133.7, 135.1, 196.0.

General procedure for the synthesis of 1,4-dihydro-tetrasubstituted pyrazines

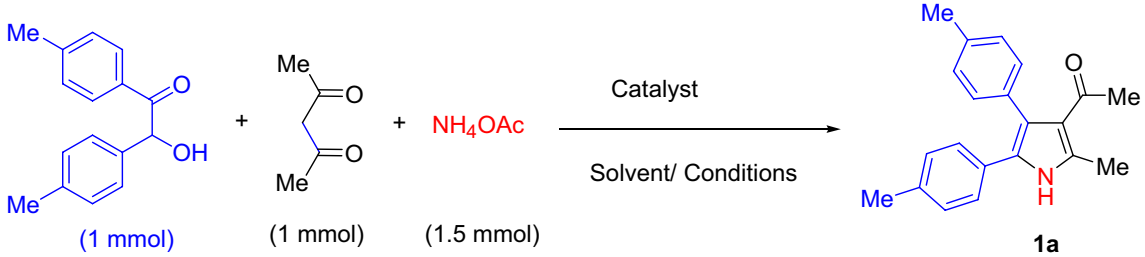
To a mixture of benzoin derivative (2 mmol), NH_4OAc (3 mmol) in ethanol (3 mL) was added acidic alumina (0.05 g, 0.05 mol %), and the mixture was refluxed for appropriative times (Table 3). After completion of the reaction (as indicated by thin-layer chromatography), warm ethanol (3 × 5 mL) was added and the catalyst was separated by filtration. The filtrated was cooled to room temperature and precipitated was filtered. For further purification, the precipitates were recrystallized from ethanol to give corresponding product.

2,3,5,6-Tetraphenyl-1,4-dihydro-pyrazine (2a) (Table 3, entry 1)

White solid; recystalized from ethanol, 70 % yield; mp >255 °C (Lit. [48] 265 °C). IR (KBr): 3193.9 (N–H), 1610.0 (cm^{-1}) (C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.21–7.56 (m, 16H, Ar), 8.08–8.10 (d, 4H, J = 7.2 Hz, Ar), 12.69 (s, 2H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 129.2, 129.6, 130.5, 138.9, 149.2. MS (EI, 70 eV): *m/z* (%) = 386 (M^+, 1.3), 385 (8.9), 384 (19.4), 383 (18.9), 298 (10.6), 297 (51.9), 296 (base peak), 295 (57.7), 178 (12.8), 165 (69.2), 97 (19.4), 89 (30.6), 83 (45.1), 71 (35.7), 57 (88.0).

2,3,5,6-Tetra-(4-methoxyphenyl)-1,4-dihydro-pyrazine (2b) (Table 3, entry 2)

White solid; recystalized from ethanol, 70 % yield; mp >255 °C. IR (KBr): 3448.5 (N–H), 1604.7 (cm^{-1}) (C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.73 (s, 12H, OCH_3), 6.88 (d, 8H, J = 5.9 Hz, Ar), 7.44 (d, 8H, J = 5.9 Hz, Ar). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 56.0, 114.6, 131.4, 131.6, 147.4, 160.4. MS (EI, 70 eV): *m/z* (%) = 508 ($M^+ + 2$, 1.1), 507 ($M^+ + 1$, 5.1), 506 (M^+, 27.1), 505 (58.4), 504 (base peak), 503 (30.8), 489 (11.8), 223 (18.7), 57 (3.1). Anal. Calcd for $C_{32}H_{30}N_2O_4$: C, 75.87; H, 5.97; N, 5.53; Found: C, 75.580; H, 5.62; N, 5.38.



Scheme 1 Preparation of 1-(2-methyl-4,5-di-*p*-tolyl-1H-pyrrole-3-yl)-ethanone

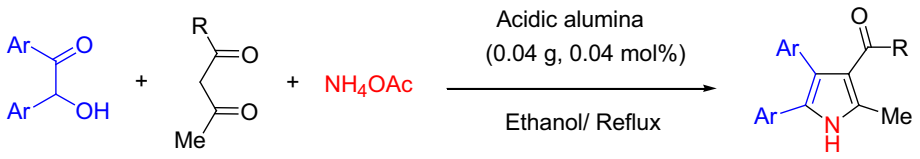
Table 1 Investigation of the effect of solvents and conditions on the synthesis of pyrrole (**1a**) in the presence different amounts of some solid acids or Lewis acids

Entry	Solvent	Catalyst loading (g)	Temperature (°C)	Time (min)	Yield (%)[a]
1	None	None	80	200	–
2	None	$FeCl_2$ (0.04 g)	80	60	20
3	None	$CuCl_2$ (0.04 g)	80	60	15
4	None	$ZnCl_2$ (0.04 g)	80	60	40
5	None	SiO_2-$TiCl_4$ (0.05 g)	80	60	10
6	None	Acidic Al_2O_3 (0.04 g)	80	60	70
7	EtOH	Basic Al_2O_3 (0.05 g)	Reflux	60	50
8	EtOH	SiO_2 (0.05 g)	Reflux	60	10
9	EtOH	Acidic Al_2O_3 (0.04 g)	60	60	45
10	EtOH	Acidic Al_2O_3 (0.04 g)	Reflux	35	88
11	EtOH	Acidic Al_2O_3 (0.04 g)	rt	60	10
12	H_2O	Acidic Al_2O_3 (0.04 g)	Reflux	60	10
13	CH_3CN	Acidic Al_2O_3 (0.04 g)	Reflux	60	60
14	$CHCl_3$	Acidic Al_2O_3 (0.04 g)	Reflux	60	Trace
15	THF	Acidic Al_2O_3 (0.04 g)	Reflux	60	Trace

Reaction conditions: 1,2-di-*p*-tolyl-ethane-1,2-dione (1 mmol), acetylacetone (1 mmol), and NH_4OAc (1.5 mmol) in solvent (3 mL)

[a] Isolated yield

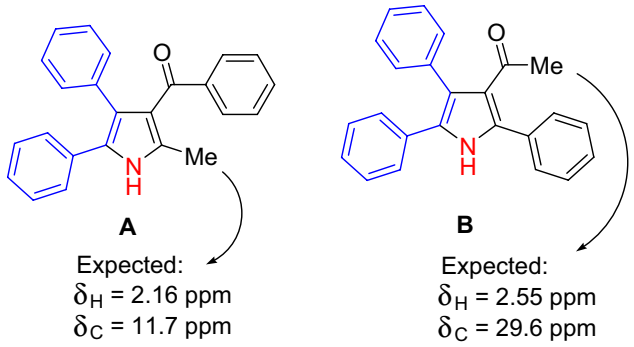
Table 2 Acidic alumina-catalyzed synthesis of tetrasubstituted pyrroles.



1 mmol 1 mmol 1.5 mmol **1a-1l**

Entry	Ar	R	Product	Time (min)	Yield (%)[a]	mp (°C)	Lit. mp (°C)
1	4-Me–C_6H_4–	Me	**1a**	35	88	237–238	237–238 [34]
2	4-Me–C_6H_4–	OMe	**1b**	35	90	175–176	–
3	4-Me–C_6H_4–	OCH_2Ph	**1c**	40	89	171–172	–
4	4-Me–C_6H_4–	Ph	**1d**	50	85	220–221	–
5	C_6H_5–	Me	**1e**	20	93	168–170	170–172 [32]
6	C_6H_5–	OEt	**1f**	20	93	203–204	206–208 [34]
7	C_6H_5–	OMe	**1g**	20	92	183–184	178–180 [34]
8	C_6H_5–	OCH_2Ph	**1h**	35	89	204–205	–
9	C_6H_5–	Ph	**1i**	50	90	218–219	223–225 [34]
10	4-F–C_6H_4–	Me	**1j**	20	90	239–240	–
11	4-F–C_6H_4–	OMe	**1k**	20	92	211–213	215–218 [38]
12	4-Cl–C_6H_4–	Me	**1l**	20	93	230–232	234–235 [32]

[a] Isolated yield



Scheme 2 Two expected regioisomers of tetrasubstituted 1*H*-pyrroles

2,3,5,6-Tetra-(4-fluorophenyl)-1,4-dihydro-pyrazine (2c) (Table 3, entry 3)

White solid; recystalized from ethanol, 70 % yield; mp >255 °C. IR (KBr): 3310.0 (N–H), 1674.8 (cm^{-1}) (N–C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.99–8.03 (m, 8H, Ar), 8.08–8.10 (m, 4H, Ar), 12.69 (s, 2H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 135.8, 159.7, 161.9, 162.1, 164.9. MS (EI, 70 eV): *m*/*z* (%) = 456 (2.6), 455 (13.1), 454 (31.6), 453 (10.4), 352 (5.6), 351 (29.3), 350 (base peak), 349 (37.1), 201 (43.9), 107 (26.1). Anal. Calcd for $C_{28}H_{18}F_4N_2$: C, 73.36; H, 3.96; F, 16.58; N, 6.11; Found: C, 73.08; H, 4.02; N, 6.03.

Results and discussion

The synthesis of highly substituted pyrroles from electron-rich benzoins is failed by acid-catalyzed methods [32, 33]. There are a few reports in the literature which able to produce highly substituted pyrroles from electron-rich benzoins [34, 38]. So, a model study was initiated with 1,2-di-*p*-tolyl-ethane-1,2-dione, acetylacetone, ammonium salts, and using various commercially acid or Lewis acid catalysts ($ZnCl_2$, $CuCl_2$, $FeCl_2$, silica, and Al_2O_3) in refluxing ethanol (Scheme 1, Table 1).

As shown in Table 1, the best results were obtained when acidic alumina was used as catalyst. In addition, basic alumina gave the corresponding product in 60 % yield after 1 h in refluxing ethanol (Table 1, entry 7).

Moreover, the model reaction was treated in different solvents such as ethanol, water, chloroform, tetrahydrofuran, and acetonitrile in the presence of acidic alumina (0.04 g, 0.04 mol %) as catalyst at refluxing conditions (Table 1, entries 9–15). Although the result under solvent-free conditions at 80 °C gave the corresponding product after 60 min in 70 % yield (Table 1, entry 6), we choose the ethanol as it is relatively benign organic solvent.

So, the optimized conditions were employed as followed: benzoin derivatives (1 mmol), acetylacetone (1 mmol), NH_4OAc (1.5 mmol), and acidic alumina (0.04 g, 0.04 mol %) in refluxing ethanol (Table 2).

As shown in Table 2, it was found that 1,3-dicarbonyl compounds such as acetyl acetone, benzoyl acetone, methyl acetoacetate, ethyl acetoacetate, and benzyl acetoacetate reacted under optimized conditions and corresponding products were obtained in high yields. In addition, it seems that benzoins bearing electron-withdrawing groups were reacted with 1,3-dicarbonyls and ammonium acetate faster than those of electron-donating ones. This may be explained according to more positive charge located on carbonyl group of these benzoins, which make them more reactive toward nucleophilic attack of nitrogen of imine intermediate [32].

To clarify mechanistic details, benzoylacetone with two different carbonyl groups from the viewpoint of steric hindrance and electrophilicity was utilized in the three-component reaction of benzoylacetone, ammonium acetate, and benzoin, followed by NMR spectroscopy. Two enaminones were expected for the reaction of each carbonyl with ammonium acetate in the first step of the reaction which would result in the formation of regioisomers **A** or **B** (Scheme 2) [34]. The ^{1}H-NMR and ^{13}C-NMR of pyrroles (**1d** and **1i**) showed the chemical shifts δ_H and δ_C at 2.16 and 12.7 for **1d** and 2.26 and 12.7 ppm for **1i**, respectively. So, they correlated with the **A** isomer.

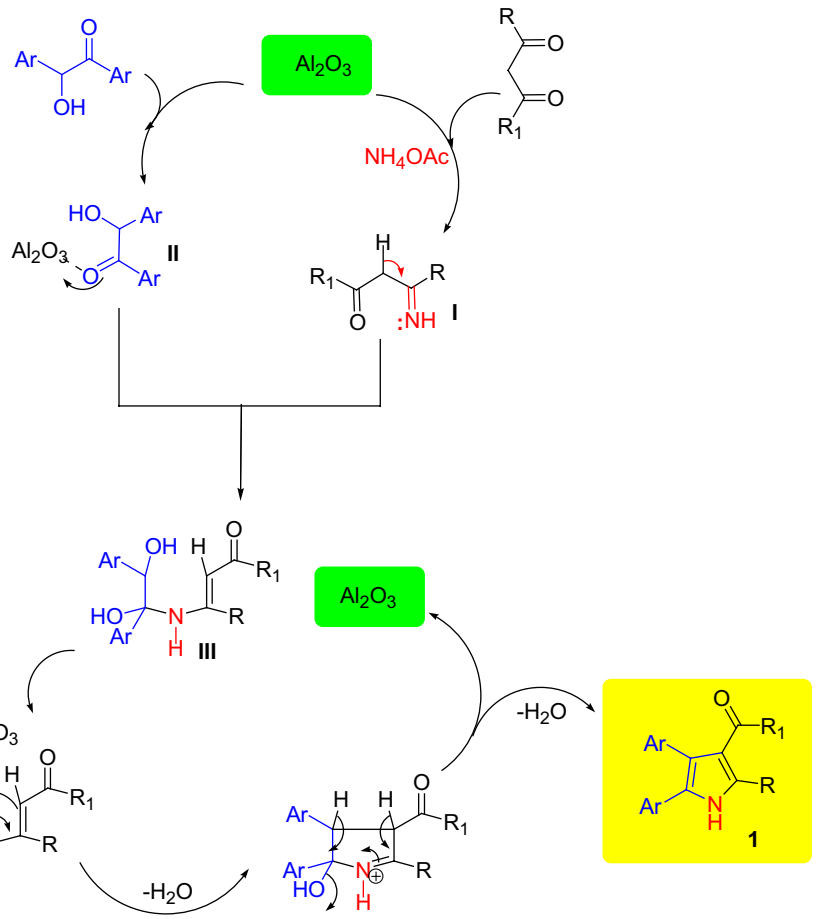
A proposed mechanism for the formation of pyrrole according to these electronic effects is outlined in Scheme 3 [32–34]. It seems that ketone group of 1,3-dicarbonyl compound reacts initially with NH_4OAc to form an imine intermediate (**I**) that subsequently condenses with activated benzoin (**II**) by acidic alumina to produce a cyclic intermediate (**III**). Dehydration of this intermediate and elimination of water produce the corresponding tetrasubstituted pyrrole (Scheme 3).

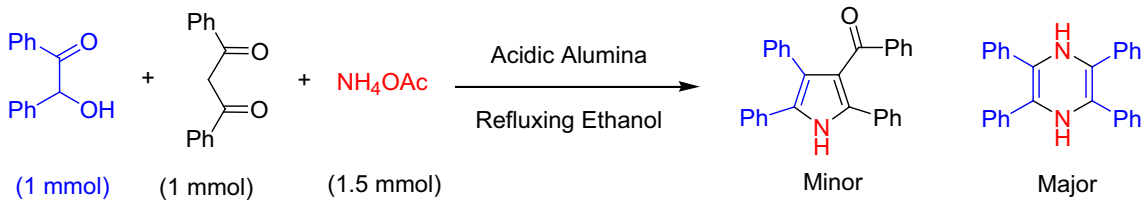
It is worth mentioning that when 1,3-diphenyl-propane-1,3-dione was treated with benzoin and ammonium acetate under optimized conditions, a by-product was the major product instead of the corresponding pyrrole (Scheme 4). After characterization, it was determined that the by-product is 1,4-dihydro-tetra-phenylpyrazine.

Also, the same product (1,4-dihydro-tetraphenylpyrazine) was obtained when 3-oxo-hexanoic acid ethyl ester was reacted with benzoin and ammonium acetate under optimized conditions.

So, we conduct the reaction without 1,3-dicarbonyl compounds as follows; benzoin (2 mmol) and ammonium acetate (3 mmol) in ethanol (3 mL) and acidic alumina (0.05 g) under reflux conditions, and the corresponding 1,4-dihydro-tetraphenylpyrazine were obtained after 100 min in 85 % yield (Table 3). As shown in Table 3,

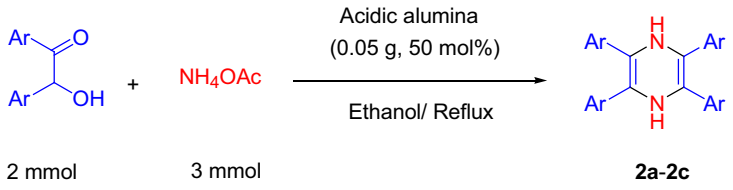
Scheme 3 Proposed mechanism for the synthesis of 2,3,4,5-tetrasubstituted pyrroles catalyzed by acidic alumina





Scheme 4 Investigation the reaction of 1,3-diphenyl-propane-1,3-dione as 1,3-dicarbonyl compound

Table 3 Acidic alumina-catalyzed synthesis of 1,4-dihydro-tetrasubstituted pyrazines.



Entry	Ar	Product	Time (min)	Yield (%)[a]	mp (°C)	Lit. mp (°C)
1	C_6H_5–	**2a**	100	85	>255	265 [48]
2	4-MeO–C_6H_4–	**2b**	100	83	>255	–
3	4-F–C_6H_4–	**2c**	100	84	>255	–

[a] Isolated yield

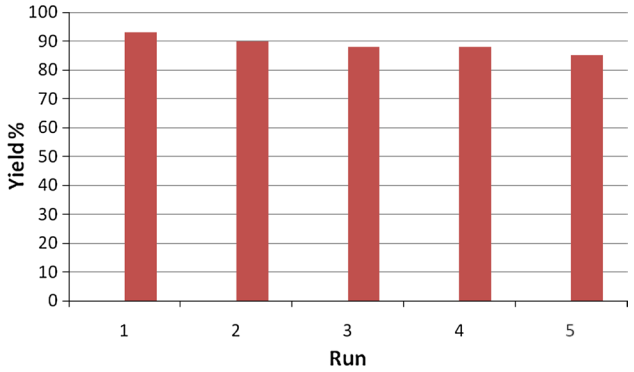


Fig. 2 Recyclability of acidic alumina in the reaction between benzoin (1 mmol), ethyl acetoacetate (1 mmol), and ammonium acetate (1.5 mmol) using alumina (0.04 g) in refluxing ethanol. Reaction time = 20 min

benzoin-substituted electron-donating group such as OMe and electron-withdrawing group such as F were converted into corresponding 1,4-dihydro-tetraarylpyrazine in high yields.

The possibility of recycling the catalyst was examined using the reaction of benzoin with ammonium acetate and ethyl acetoacetate under optimized conditions. Upon completion, the reaction mixture was filtered and the solid was washed with warm ethanol, and recycled catalyst was saved for next reaction. The recycled catalyst could be reused up to four times without any treatment (Fig. 2).

Conclusions

In conclusion, this work shows acidic alumina which is commercially available, efficiently catalyzed the synthesis of 2,3,4,5-tetrasubstituted pyrroles via the condensation reaction of benzoins, 1,3-dicarbonyl compounds, and ammonium acetate in refluxing ethanol in high yields. Acidic alumina could be recovered and reused for several times without noticeable loss of reactivity.

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