Heterocycl. Commun., Vol. 17(1-2), pp. 79–81, 2011 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/HC.2011.018

New approach to the multicomponent one-pot synthesis of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles

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Abstract

A novel, acid catalyzed multicomponent one-pot synthesis of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole compounds derived from aromatic aldehydes, 9,10-phenanthrenequinone and ammonium acetate under ultrasonic irradiation is reported. A wide range of aromatic aldehydes readily undergo condensation with 9,10-phenanthrenequinone and ammonium acetate under optimized conditions to afford the desired imidazoles of good purity in excellent yields.

Keywords: 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole; one-pot synthesis; ultrasonic irradiation.

Introduction

One-pot multicomponent reactions (MCRs) that convert more than two reactants directly into their products are of interest to chemists, owing to conserving atom economy and fostering the benign synthesis of organic compounds. MCRs are part of the latest advanced solutions for decreasing the discovery and development times for new drugs, and potentially reducing the development costs and complexity in the process. Thus, useful structural variations can be increased (Weber et al., 1999; Bienayme et al., 2000).

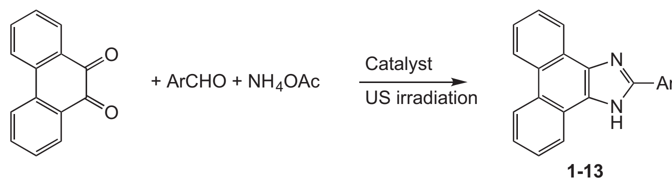
Compounds with an imidazole moiety have biological and pharmaceutical importance. For example, several substituted imidazoles are inhibitors of p38 MAP kinase (Lee et al., 1994). Highly substituted imidazoles such as lepidilines exhibit micromolar cytotoxicity against several human cancer cell lines (Cui et al., 2003). Trifenagrel is a potent 2,4,5-triarylimidazole that reduces platelet aggregation in several animal species and humans (Abrahams et al., 1989).

In 1882, Radziszewski and Japp reported the first synthesis of 2,4,5-triphenylimidazoles from the reaction of 1,2-dicarbonyl compounds with various aldehydes and ammonia (Radziszewski, 1882). Recently, a literature survey reveals several methods for the synthesis of 2,4,5-triarylimidazoles using boric acid (Shelke et al., 2009), zeolite HY/silica gel (Balalaie and Arabanian, 2000), tetrabutylammonium bromide (Salehi et al., 2011), sulfanilic acid (Mohammed et al., 2007), ionic liquid (Siddiqui et al., 2005), and $InCl_3 \cdot 3H_2O$ (Sharma et al., 2008). These examples utilized a one-pot three-component reaction of 1,2-dicarbonyl compounds, aldehydes, ammonium acetate, and various catalysts. However, benzil and benzoin compounds were mainly examined for the synthesis of 2,4,5-triphenylimidazoles. In the present study, the reaction of 9,10-phenanthrenequinone with various aromatic aldehydes and ammonium acetate under ultrasonic irradiation using various catalysts was examined, and the corresponding 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole derivatives **1–13** were obtained in excellent yields (Scheme 1).

Results and discussion

In our initial search for appropriate reaction conditions, we chose the reaction of benzaldehyde, 9,10-phenanthrenequinone and ammonium acetate as a model. The reactions were conducted with a variety of catalysts and solvents as depicted in Table 1. In entries 1–8, the catalytic efficiency of $Yb(OTf)_3$, $La(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, HOTf, CH_3SO_3H, CF_3COOH and *p*-toluenesulfonic acid (*p*-TSA) was studied. In all cases 5 mol % of the catalyst was used and the reaction was carried out in ethanol and under ultrasonic irradiation. As shown in Table 1, the best result was obtained when *p*-TSA was used as a catalyst (entry 8). The effects of the solvent on the reaction were also investigated as indicated by entries 8–14 in Table 1. The best results were obtained for the reaction conducted in ethanol and acetonitrile (entries 8 and 14, respectively). Accordingly, ethanol was chosen as the solvent for further reactions.

To generalize the scope of this reaction and its utility as a new synthetic approach to 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole derivatives **1–13**, the methodology was extended by including 13 different aromatic aldehydes. The aldehydes contain electron withdrawing groups (such as nitro group, halogen) or electron-donating groups (such as methoxy group), and in each case moderate to excellent yields of the desired products were obtained under the optimized conditions; hence, demonstrating the versatility of the methodology. It is worthy to note that the condensation of 2-chlorobenzaldehyde and 2-flurobenzaldehyde afforded the desired 2-(4-chloro)-1-*H*-phenanthro[9,10-*d*]imidazole and 2-(2-fluorophenyl)-1-*H*-phenanthro[9,10-*d*]imidazole, respectively (**9**, **10**) in good yield indicating that steric hindrance is not a factor in this reaction. The reaction of 1-naphthalenecarboxaldehyde also gave the corresponding product **11** in high yield. The mechanism for this reaction is likely to involve the formation of an aminal intermediate, followed by condensation with 9,10-phenanthrenequinone, intramolecular cyclization, and subsequently



Ar=C_6H_5 - (**1**); 4-$NO_2C_6H_4$ - (**2**); 4-$CH_3OC_6H_4$ - (**3**); 4-ClC_6H_4 - (**4**); 4-$CH_3C_6H_4$ - (**5**);
4-HOC_6H_4 - (**6**); 4-(N,N-dimethyl)C_6H_4 - (**7**); 2-furanyl - (**8**); 2-ClC_6H_4 - (**9**);
2-FC_6H_4 - (**10**); 1-naphthyl - (**11**); 3-ClC_6H_4 - (**12**); 2,4-dimethylC_6H_4 - (**13**)

Scheme 1 Synthesis of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole derivatives **1–13**.

[1,5] sigmatropic proton shift to afford the corresponding 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole derivative.

Conclusion

We have developed a novel, efficient, ultrasonic irradiation, and *p*-TSA catalyzed method for the synthesis of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole derivatives by a one-pot three-component reaction of aldehyde, 9,10-phenanthrenequinone and ammonium acetate. Particularly valuable features of this synthetic process are excellent yields, mild reaction conditions, easy work-up, and short reaction time.

Experimental

General

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka, and Aldrich Chemical Companies. All yields refer to isolated products. The IR spectra were recorded in KBr disks on a Shimadzu-IR 470 spectrophotometer and the results are reported in cm^{-1}. The ^1H NMR spectra were recorded on a Bruker 100-MHz spectrometer in DMSO-d_6 as the solvent with TMS as internal standard. Sonication was performed in a Shanghai Branson-CQX ultrasonic cleaner with a frequency of 40 kHz and a nominal power of 100 W. Flash column chromatography was performed with 300- and 400-mesh silica gel, and analytical thin layer chromatography was performed on precoated silica gel plates (60F-254). Elemental analyses were performed on a Thermo Finnigan EA1112 elemental analyzer.

Table 1 2-Aryl-1*H*-phenanthro[9,10-*d*]imidazole synthesis catalyzed by different catalysts under ultrasonic irradiation.

Entry	Catalyst	Solvent	Yield (%)[a,b]
1	$Yb(OTf)_3$	EtOH	88
2	$La(OTf)_3$	EtOH	85
3	$Cu(OTf)_2$	EtOH	80
4	$Zn(OTf)_2$	EtOH	82
5	HOTf	EtOH	80
6	CH_3SO_3H	EtOH	84
7	CF_3COOH	EtOH	88
8	*p*-TSA	EtOH	94
9	*p*-TSA	$ClCH_2CH_2Cl$	93
10	*p*-TSA	CH_2Cl_2	78
11	*p*-TSA	CH_3OH	88
12	*p*-TSA	THF	82
13	*p*-TSA	Toluene	75
14	*p*-TSA	CH_3CN	92

[a]Reaction conditions: solvent (10 ml), benzaldehyde (1 mmol), 9,10-phenanthrenequinone (1 mmol), ammonium acetate (3.5 mmol), 5 mol % of catalyst, room temperature and under US irradiation (6 min).
[b]Isolated yield.

General procedure for preparation of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazole derivatives

A mixture of aromatic aldehyde (1 mmol), 9,10-phenanthrenequinone (1 mmol), ammonium acetate (3.5 mmol), and 5 mol % of *p*-TSA in ethanol (10 ml) was stirred at room temperature under ultrasonic irradiation using ultrasonic cleaner with a frequency of 40 KHz and a nominal power 100 W for the appropriate time. After completion of the reaction, as indicated by TLC, the catalyst was removed by filtration and evaporation of the solvent afforded the crude product, which was purified by silica gel column chromatography using petroleum ether/ethyl acetate (9:1). The selected compounds are characterized as follows.

2-Phenyl-1*H*-phenanthro[9,10-*d*]imidazole (1) After 6 min the yield was 94%; mp 328–330°C; IR: 3405 (N-H), 1552 (C=C), 1590 (C=N); ^1H NMR: δ 6.95–7.45 (m, 9H, Ar), 7.75 (d, 2H, *J*=7.5 Hz), 8.10 (d, 2H, *J*=5.2 Hz), 12.25 (s, NH). Analysis calculated for $C_{21}H_{14}N_2$: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.33; H, 4.55; N, 9.44.

2-(4-Nitrophenyl)-1*H*-phenanthro[9,10-*d*]imidazole (2) After 8 min the yield was 93%; mp 336–338°C; IR: 3435 (N-H), 1555 (C=C), 1585 (C=N), 1340 (NO_2), 1525 (NO_2); ^1H NMR: δ 7.10–7.65 (m, 10H, Ar), 8.04 (d, 2H, *J*=8 Hz), 11.95 (s, 1H, NH). Analysis calculated for $C_{21}H_{13}N_3O_2$: C, 74.25; H, 3.90; N, 12.22. Found: C, 74.33; H, 3.86; N, 12.38.

2-(4-Methoxyphenyl)-2*H*-phenanthro[9,10-*d*]imidazole (3) After 5.5 min the yield was 91%; mp 255–256°C; IR: 3405 (N-H), 1552 (C=C), 1590 (C=N); ^1H NMR: δ 3.72 (s, 3H), 6.90–7.35 (m, 8H, Ar), 7.88 (d, 2H, *J*=7.5 Hz), 8.10 (d, 2H, *J*=7.5 Hz), 12.30 (s, NH). Analysis calculated for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 80.95; H, 4.90; N, 8.55.

2-(4-Chlorophenyl)-1*H*-phenanthro[9,10-*d*]imidazole (4) After 6.5 min the yield was 92%; mp 275–276°C; IR: 3420 (N-H), 1425–1540 (C=C), 1595 (C=N). ^{1}H NMR 7.05–7.55 (m, 8H, Ar), 7.6–7.95 (m, 2H, Ar), 8.10 (d, 2H, *J*=7 Hz), 12.14 (s, NH). Analysis calculated for $C_{21}H_{13}ClN_2$: C, 76.71; H, 3.99; N, 8.52. Found: C, 76.61; H, 3.98; N, 8.46.

2-*p*-Tolyl-1*H*-phenanthro[9,10-*d*]imidazole (5) After 7 min the yield was 92%; mp 270–271°C; IR: 3405 (N-H), 1425–1525 (C=C), 1605 (C=N); ^{1}H NMR: δ 2.20 (s, 3H), 7.10–7.50 (m, 8H, Ar), 7.70–7.90 (m, 2H, Ar), 8.05 (d, 2H, *J*=5.2 Hz), 12.10 (s, NH). Analysis calculated for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.08. Found: C, 85.60; H, 5.20; N, 8.97.

2-(4-Hydroxyphenyl)-1*H*-phenanthro[9,10-*d*]imidazole (6) After 7 min the yield was 90%; mp 350–352°C; IR: 3345 (N-H), 1415–1530 (C=C), 1609 (C=N); ^{1}H NMR: δ 6.95–7.55 (m, 6H, Ar), 7.67–7.86 (m, 4H, Ar), 8.02 (d, 2H, *J*=4.5 Hz), 9.75 (s, OH), 13.10 (s, NH). Analysis calculated for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55; N, 9.03. Found: C, 80.96; H, 4.51; N, 8.97.

2-(4-*N,N*-dimethylanilino)-1*H*-phenanthro[9,10-*d*]imidazole (7) After 6 min the yield was 92%; mp 266–268°C; IR: 3510 (O-H, N-H), 1420–1552 (C=C), 1592 (C=N); ^{1}H NMR: δ 2.90 (s, Me), 3.05 (s, Me), 7–7.75 (m, 7H, Ar), 7.80–8.10 (m, 5H, Ar), 12.10 (s, NH). Analysis calculated for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.81; H, 5.65; N, 12.38.

2-(Furan-2-yl)-1*H*-phenanthro[9,10-*d*]imidazole (8) After 7 min the yield was 88%; an oil; IR: 3410 (N-H), 1415–1530 (C=C), 1608 (C=N); ^{1}H NMR: δ 7.07–7.55 (m, 7H, Ar), 7.70–8.05 (m, 2H, Ar), 8.15 (d, 2H, *J*=5.2 Hz), 12.12 (s, NH). Analysis calculated for $C_{19}H_{12}N_2O$: C, 80.27; H, 4.25; N, 9.85. Found: C, 80.02; H, 4.21; N, 9.79.

2-(2-Chlorophenyl)-1*H*-phenanthro[9,10-*d*]imidazole (9) After 7.5 min the yield was 91%; an oil; IR: 3385 (N-H), 1416–1605 (C=C), 1635 (C=N). ^{1}H NMR δ 7.05–7.50 (m, 4H, Ar), 7.70–8.10 (m, 8H, Ar), 11.95 (s, NH). Analysis calculated for $C_{21}H_{13}N_2Cl$: C, 76.71; H, 3.99; N, 8.52. Found: C, 76.55; H, 3.91; N, 8.55.

2-(2-Fluorophenyl)-1*H*-phenanthro[9,10-*d*]imidazole (10) After 7 min the yield was 90%; mp 320–322°C; IR: 3440 (N-H), 1465–1614 (C=C), 1630 (C=N); ^{1}H NMR: δ 6.90–7.40 (m, 5H, Ar), 7.60–7.85 (m, 5H, Ar), 8.10 (d, 2H, *J*=7 Hz), 12.10 (s, NH). Analysis calculated for $C_{21}H_{13}N_2F$: C, 80.75; H, 4.20; N, 8.97. Found: C, 80.64; H, 4.19; N, 8.94.

2-(Naphthalen-1-yl)-1*H*-phenanthro[9,10-*d*]imidazole (11) After 8 min the yield was 94%; an oil; IR: 3390 (N-H), 1414–1536 (C=C), 1602 (C=N); ^{1}H NMR: δ 7–7.50 (m, 6H, Ar), 7.75–8.15 (m, 9H, Ar), 12.12 (s, NH). Analysis calculated for $C_{25}H_{16}N_2$: C, 87.18; H, 4.68; N, 8.13. Found: C, 87.08; H, 4.61; N, 8.02.

2-(3-Chlorophenyl)-1*H*-phenanthro[9,10-*d*]imidazole (12) After 6.5 min the yield was 93%; mp 305–307°C; IR: 3425 (N-H), 1410–1625 (C=C), 1640 (C=N); ^{1}H NMR: δ 7.10–7.55 (m, 6H, Ar), 7.65–8.0 (m, 6H, Ar), 12.03 (s, NH). Analysis calculated for $C_{21}H_{13}N_2Cl$: C, 76.71; H, 3.99; N, 8.52. Found: C, 76.63; H, 4.04; N, 8.51.

2-(2,4-Dimethylphenyl)-1*H*-phenanthro[9,10-*d*]imidazole (13) After 6 min the yield was 93%; mp 277–278°C; IR: 3410 (N-H), 1405–1655 (C=C), 1660 (C=N); ^{1}H NMR: δ 2.25 (s, 3H, Me), 2.30 (s, 3H, Me), 7.10–7.40 (m, 5H, Ar), 7.55–8.15 (m, 7H, Ar), 12.15 (s, NH). Analysis calculated for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.58; H, 5.59; N, 8.62.

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Received April 28, 2011; accepted May 24, 2011