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Base-promoted cyclocondensation of (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones with guanidine hydrochloride: facile synthesis of *E*-2-amino-4-aryl-6-(2-arylethenyl)pyrimidines

Abstract

Base-promoted cyclocondensation of symmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones (1) with guanidine hydrochloride has been found to generate *E*-2-amino-4-aryl-6-(2-arylethenyl)pyrimidines (3) in good yield, the structures of which have been established from analytical and spectral data. The corresponding unsymmetrical analogues (2), however, were found to produce a mixture of two isomeric products non-regioselectively.

Keywords: (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones, guanidine hydrochloride, sodium hydroxide, e-2-amino-4-aryl-6-(2-arylethenyl)pyrimidines

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Introduction

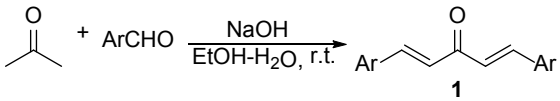
A considerable attention has been focused on synthesis of various substituted pyrimidines due to their interesting biological activities.[1–3] Aminopyrimidines constitute one of the important classes of pyrimidines. The pharmaceutical importance of these compounds lies on the fact that they can be effectively used as analgesics, anti-inflammatory, anticonvulsant, insecticidal, herbicidal, antitubercular, anticancer and antidiabetic agents.[4–6] Also, the pyrimidine and aminopyrimidine structures are frequently-occurring motifs in commercially available drugs such as anti-atherosclerotic aronixil,[7] anti-anxiolytic buspirone,[8] and other medicinally relevant compounds.[9,10] Symmetrical (1E,4E)-1,5-diarylpenta-1,4-dien-3-ones (1) and their unsymmetrical analogues (2), which could be constructed easily, also possess structural features similar to α,α'-bis(arylmethylene)cycloalkanones previously utilized by us for studying their reaction with thiourea and guanidine hydrochloride.[11,12] It is evident from the literature that the reaction of (1E,4E)-1,5-diarylpenta-1,4-dien-3-ones (1 and 2) with guanidine has not been studied so far, although there are reports of cyclocondensation of varieties of α,β-unsaturated ketones with guanidine.[13,14] In this paper, we report a facile synthesis of E-2-amino-4-aryl-6-(2-arylethenyl) pyrimidines by base-promoted cyclocondensation of various (1E,4E)-1,5-diarylpenta-1,4-dien-3-ones with guanidine hydrochloride.

Materials and methods

Reagents were purchased (Spectrochem or SRL) and used without further purification. Melting points were determined on a Köfler block and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ on Bruker AV-300 (300MHz and 75MHz, respectively) spectrometer using TMS as an internal standard. Analytical samples were dried *in vacuo* at room temperature. The carbon, hydrogen and nitrogen percentages in the synthesized products were analyzed by using two Perkin-Elmer 2400 series II C, H, N analyzers. HRMS were recorded on a Waters Xevo G2QT mass spectrometer. Thin layer chromatography was carried out on silica gel G.

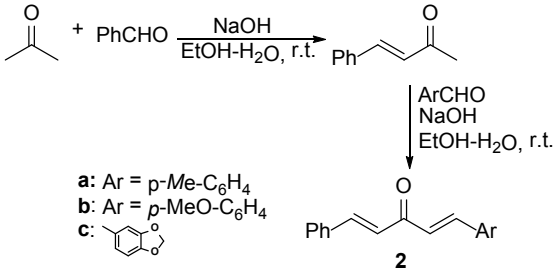
Synthesis of (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones (1 and 2)

The symmetrical compounds (1) were prepared by base-catalyzed condensation of benzalde-hydes and acetone in 2:1 mole ratio (Scheme 1).[15] The unsymmetrical compounds (2) were obtained by two successive condensation steps–(E)-4-phenylbut-3-en-2-one was first prepared by a known method and then subjected to base-catalyzed condensation with benzaldehydes (Scheme 2).[15] They were characterized from their spectral data.



a: Ar = C_6H_5; **b**: Ar = *p*-Me-C_6H_4
c: Ar = *p*-Cl-C_6H_4; **d**: Ar = *p*-MeO-C_6H_4

Scheme 1 Synthesis of symmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones.



Scheme 2 Synthesis of unsymmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones.

General procedure for base-promoted reaction of (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones (1 and 2) with guanidine hydrochloride

A mixture of 1 or 2 (1mmol), guanidine hydrochloride (1mmol), sodium hydroxide (5mmol) and ethanol (20ml) was refluxed for 2h. The mixture was poured into ice cold water after completion of the reaction. The solid thus obtained was filtered off, washed with water until it was free from alkali. The crude product was extracted with chloroform and dried over anhydrous sodium sulphate. The concentrate of the chloroform extract was chromatographed over silica gel using petroleum ether-ethyl acetate (4:1) as eluent. Spectral data of the synthesized compounds were as follows:

***E*-2-Amino-4-phenyl-6-(2-phenylethenyl)-pyrimidine (3a):** Yield: 65%, m.p. 128-130°C; IR: ν_{max} 3320 and 3198 (NH_2), 3005, 1632, 1575, 1350, 1160, 821cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ5.20 (2H, br. s, NH_2), 7.02 (1H, d, J=16.2Hz, C=C-H), 7.12 (1H, s, H-5 of pyrimidine moiety), 7.31-7.42 (3H, m, Ar-H), 7.49 (3H, br. s, Ar-H), 7.60 (2H, d, J=6.9Hz, Ar-H), 7.83 (1H, d, J=16.1Hz, H- C=C), 8.03 (2H, br. s, Ar-H). ^{13}C NMR (75MHz, $CDCl_3$): δ106.14, 126.05, 127.13 (2 carbons), 127.62 (2 carbons), 128.79 (2 carbons), 128.84 (2 carbons), 129.22, 130.66, 135.89, 136.62, 137.28, 162.92, 163.68, 166.24. HRMS for $C_{18}H_{16}N_3$ $(M+H)^+$: Calcd. 273.1344, Found. 274.1338. Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37%. Found C, 79.01; H, 5.69; N, 15.18%.

***E*-2-Amino-4-(p-methylphenyl)-6-(2-p-methyl--phenylethenyl)pyrimidine (3b):** Yield: 61%, m.p. 142-143°C; IR: ν_{max} 3343 and 3200 (NH_2), 2922, 1638, 1570, 1364, 1180, 1116, 818cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ2.38 (3H, s. Ar-CH_3), 2.42 (3H, s, Ar-CH_3), 5.11 (2H, br. s, NH_2), 6.95 (1H, d, J=15.9Hz, C=-C-H), 7.08 (1H, s, H-5 of pyrimidine moiety), 7.20 (2H, d, J=8.1Hz, Ar-H), 7.29 (2H, d, J=8.1Hz, Ar-H), 7.49 (2H, d, J=7.8Hz, Ar-H), 7.79 (1H, d, J=15.9, H-C=C), 7.93 (2H, d, J=7.8Hz, Ar-H). HRMS for $C_{20}H_{20}N_3$ $(M+H)^+$: Calcd. 302.1657, Found. 302.1678. Anal. Calcd. for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94%. Found C, 79.51; H, 6.50; N, 13.66%.

***E*-2-Amino-4-(p-chlorophenyl)-6-(2-p-chloro-phenylethenyl)pyrimidine (3c):** Yield: 75%, m.p. 212-214°C; IR: ν_{max} 3349 and 3205 (NH_2), 2923, 1651, 1560, 1359, 1196, 826cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ5.10 (2H, br. s, NH_2), 6.97 (1H, d, J=15.9Hz, C=C-H), 7.05 (1H, s, H-5 of pyrimidine moiety), 7.37 (2H, d, J=8.4Hz, Ar-H), 7.46 (2H, d, J=8.4Hz, Ar-H), 7.52 (2H, d, J=8.7Hz, Ar-H), 7.77 (1H, d, J=15.9Hz, H-C=C), 7.98 (2H, d, J=8.4Hz, Ar-H). Anal. Calcd. for $C_{18}H_{13}N_3Cl_2$: C, 63.17; H, 3.83; N, 12.28%. Found C, 63.01; H, 3.60; N, 12.51%.

***E*-2-Amino-4-(p-methoxyphenyl)-6-(2-p-methoxyphenylethenyl)pyrimidine (3d):** Yield: 58%, m.p. 152-153°C; IR: ν_{max} 3330 and 3189 (NH_2), 2932, 1651, 1636, 1605, 1512, 1252, 1173, 828cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ3.85 (3H, s. Ar-OCH_3), 3.88 (3H, s, Ar-OCH_3), 5.07 (2H, br. s, NH_2), 6.87 (1H, d, J=16.0Hz, C=C-H), 6.93 (2H, d, J=8.7Hz, Ar-H), 6.99 (2H, d, J=9.0Hz, Ar-H), 7.04 (1H, s, H-5 of pyrimidine moiety), 7.54 (2H, d, J=8.7Hz, Ar-H), 7.77 (1H, d, J=15.9Hz, H-C=C), 8.01 (2H, d, J=8.7Hz, Ar-H). Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60%. Found C, 71.92; H, 5.59; N, 12.42%.

Mixture of compounds 4a and 5a: IR: ν_{max} 3341, 3210, 3051, 2986, 1632, 1580, 1363, 1170, 828cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ2.38 (approx. 1.2H, s, Ar-CH_3 of one component), 2.42 (approx. 1.8H, s, Ar-CH_3 of the other component), 5.29 (2H, br. s, NH_2 of both the components), 7.03-8.04 (approx. 12H, m, aromatic and olefinic protons). HRMS for $C_{19}H_{18}N_3$ $(M+H)^+$: Calcd. 288.1501, Found. 288.1514.

Mixture of compounds 4b and 5b: IR: ν_{max} 3350, 3200, 3041, 2950, 1645, 1612, 1542, 1175, 830cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ3.82 (approx. 1.5H, s, Ar-OCH_3 of one component), 3.85 (approx. 1.5H, s, Ar-OCH_3 of the other component), 5.09 (2H, br. s, NH_2 of both the components), 6.86-8.04 (approx. 12H, m, aromatic and olefinic protons).

Mixture of compounds 4c and 5c: IR: ν_{max} 3368, 3198, 2956, 1623, 1600, 1576, 1185, 991, 832cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ5.00-5.10 (2H, m, NH_2 of both the components), 6.01 (approx. 0.8H, s, –OCH_2O- of one component), 6.04 (approx. 1.2H, s, –OCH_2O- of the other component), 6.65-8.02 (approx. 11H, m, aromatic and olefinic protons).

Results and discussion

Symmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones (1a-d) were chosen first for carrying out the targeted reaction. When each of these (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones (1mol) was treated with guanidine hydrochloride (1mol or 2mol) in 10% ethanolic sodium hydroxide. Under refluxing condition. The reaction proceeded smoothly and was found to be complete within 2h. Product isolation from the reaction mixture with each of 1a-d through work up in the usual way (vide Experimental) followed by purification by column chromatograpy over silica gel furnished a single product in good yield (Scheme 3) (Table 1). Analytical and spectral data of the products definitely showed that only 1:1 cyclocondensation took place resulting in the formation of the hitherto unknown compounds *E*-2-amino-4-aryl-6-(2-arylethenyl) pyrimidines (3). The reaction of the unsymmetrical compounds 2a-c with guanidine hydrochloride was then studied by using the similar reaction conditions (Scheme 4).

Table 1 Results of cyclocondensation of symmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones with guanidine hydrochloride

Entry	Starting material	Product	Yield (%)	M.p. (°C)
1	1a	3a	65	128-130
2	1b	3b	61	142-143
3	1c	3c	75	212-214
4	1d	3d	58	152-153

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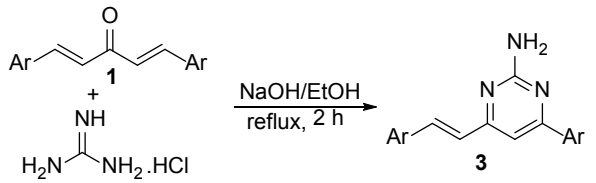
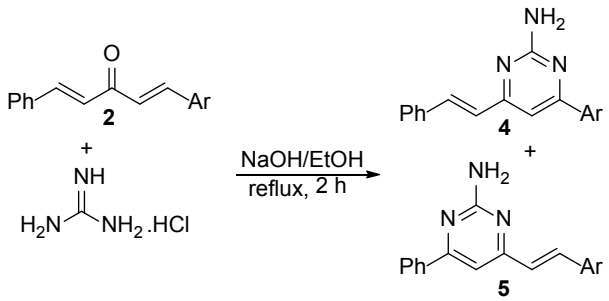
In case of the unsymmetrical starting materials 2a-c, the reaction was not at all regioselective, and it was evident from the ^{1}H NMR spectral features of the resulting materials obtained after passing the concentrate of the reaction mixtures through chromatography columns in the usual way that a mixture of two isomeric products 4 and 5 in the approximate ratio 3:2 to 1:1 (Table 2) was formed in these cases. These two isomeric compounds could not be separated by exhaustive column chromatograpy over silica gel as well as over neutral alumina. Attempted separation by preparative chromatograpy over silica gel as well as neutral alumina also did not meet with success.

Table 2 Results of cyclocondensation of unsymmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones with guanidine hydrochloride

Entry	Starting material	Products (approx. ratio)[a]	Total yield (%)	Melting range (°C)
1	2a	4a and 5a (3:2)[b]	65	134-140
2	2b	4b and 5b (1:1)	72	120-128
3	2c	4c and 5c (3:2)[b]	68	88-95



Scheme 3 Reaction of symmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones with guanidine.



Scheme 4 Reaction of unsymmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones with guanidine.

Conclusion

In conclusion, we have developed a simple and convenient method for synthesis of E-2-amino-4-aryl-6-(2-arylethenyl) pyrimidines, a group of hitherto unknown 2-aminopyrimidines, by base-promoted condensation of (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones with guanidine hydrochloride. However, involvement of several unsymmetrical (1*E*,4*E*)-1,5-diarylpenta-1,4-dien-3-ones in this process with a view to increasing the structural variation of such products was not successful as no regioselectivity was observed in these cases.

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Conflict of interest

The author declares no conflict of interest.

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