An Expeditious and Solvent-Free Synthesis of 2-Amino-Substituted Isoflav-3-enes Using Microwave Irradiation†

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Introduction

Isoflav-3-enes bearing a 2*H*-1-benzopyran nucleus form an important class of chromene intermediates useful in the synthesis of many natural products and medicinal agents such as potassium-channel activating drugs.[1] Their basic structural framework is a common feature of many tannins and polyphenols[2] found in fruits, vegetables, teas, and red wines which have gained popularity because of their health-promoting effects. Additionally, isoflav-3-enes are well-known estrogens,[3] and several derivatives of these oxygen heterocycles have attracted the attention of medicinal chemists over the years. In view of our ongoing endeavors to conduct organic synthesis under solvent-free conditions,[4] we decided to adopt an enamine-mediated approach for the one-pot assembly of isoflav-3-enes substituted at the 2-position with various cyclic amines.[5]

Enamines **4** are usually prepared by the condensation of a carbonyl compound bearing an α-hydrogen atom **1** with a secondary amine **2** followed by the dehydration of the resultant intermediate **3** (Scheme 1).[6−8] The azeotropic removal of water from the intermediate **3** is the driving force for the reaction which is normally catalyzed by reagents such as *p*-toluenesulfonic acid,[6] titanium(IV) chloride,[7] montmorillonite K-10 clay,[8] etc., in a Dean−Stark setup requiring a large excess of aromatic hydrocarbon solvents such as benzene or toluene. We have recently demonstrated the advantageous attributes of microwave-assisted elimination of water in the rapid and solvent-free synthesis of enamines[4i,j] and nitroalkenes.[4k]

Since the appearance of the first paper on the application of microwave irradiation in the chemical synthesis,[9] the approach has blossomed into a useful technique for a variety of applications in organic synthesis and functional group transformations.[4,10,11] The initial experiments with microwave techniques centered around the use of high dielectric solvents such as DMSO and DMF in specialized Teflon vessels and sealed containers. The rate enhancements in such reactions are now believed to be essentially due to rapid superheating of these polar solvents. The focus has now shifted to less cumbersome solvent-free methods wherein the neat reactants, often in the presence of mineral supports, undergo facile reactions to provide high yields of pure products, thus eliminating or minimizing the use of organic solvents.[4,10f,11] The bulk temperature is relatively low in such solventless reactions, although higher localized temperatures may be reached during microwave irradiation.

Earlier, we discovered a general route to isoflav-3-enes[5] that, contrary to previous findings,[12] proceeds readily via

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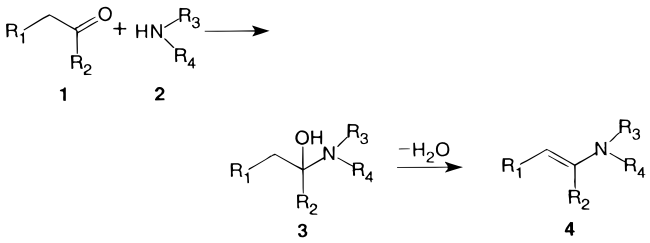
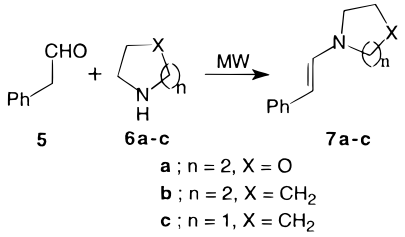
Scheme 1



Scheme 2



a ; n = 2, X = O
b ; n = 2, X = CH_2
c ; n = 1, X = CH_2

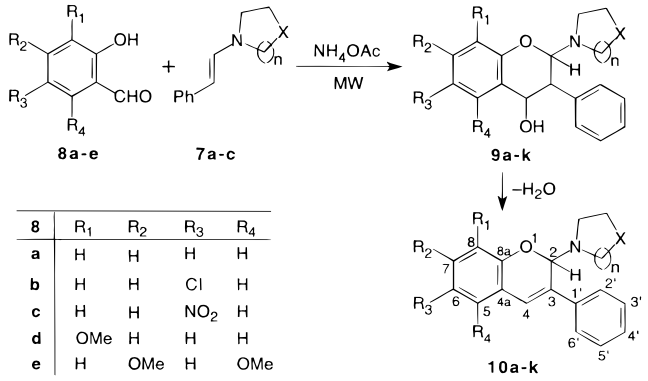
the condensation of *N*-styrylamines with *o*-hydroxyarylaldehydes to deliver 2-substituted isoflav-3-ene derivatives. In an extension of our present program to develop efficient solventless protocols,[4] we decided to pursue the synthesis of 2-amino(2-morpholino, 2-piperidino, and 2-pyrrolidino)-substituted isoflav-3-enes under solvent-free conditions using microwaves. Herein, we report our results that exploit the in situ generation of enamine intermediates that can be further elaborated, in one-pot protocol, to 2-substituted isoflav-3-enes **10a**−**k** from readily accessible phenyl acetaldehyde (**5**), cyclic amines **6a**−**c**, and salicylaldehydes **8a**−**e** in the presence of ammonium acetate as a catalyst.

Results and Discussion

In the first step, the enamines *N*-styrylmorpholine, **7a**,[13] *N*-styrylpiperidine, **7b**,[14] and *N*-styrylpyrrolidine, **7c**,[15] are prepared within 2 min by irradiating a mixture of phenyl acetaldehyde with respective cyclic amines **6a**−**c** in open glass containers using an unmodified household microwave oven (Scheme 2). The addition of salicylaldehydes to the same reaction vessel, in the second step, and further exposure to microwaves generates the desired isoflav-3-enes. The present procedure considerably reduces the longer reaction time usually encountered in traditional enamine synthesis, which employs a large excess of aromatic hydrocarbon solvents for the azeotropic removal of water using a Dean−Stark apparatus.[6−8]

In our previously described solution-phase chemistry, the reaction of enamine **7a** with substituted salicylaldehydes **8a** and **8d** in benzene under an inert atmosphere produced 2-morpholinoisoflav-3-ene **10a** and 8-methoxy-2-morpholinoisoflav-3-ene **10d** in 55 and 45.6% yields, respectively (Scheme 3).[5] The same reactions under solvent-free conditions using microwaves in the presence of ammonium acetate as a catalyst (0.25 mmol), however, provide the desired products expeditiously in 80 and 73% yields, respectively. A pulsed microwave technique is

Scheme 3



8	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	H	Cl	H
c	H	H	NO_2	H
d	OMe	H	H	H
e	H	OMe	H	OMe

Table 1. One-Pot Synthesis of Isoflav-3-enes

entry	substitution at C-2	R_1	R_2	R_3	R_4
10a	morpholinyl	H	H	H	H
10b	morpholinyl	H	H	Cl	H
10c	morpholinyl	H	H	NO_2	H
10d	morpholinyl	OMe	H	H	H
10e	morpholinyl	H	OMe	H	OMe
10f	piperidinyl	H	H	H	H
10g	piperidinyl	H	H	Cl	H
10h	piperidinyl	H	H	NO_2	H
10i	pyrrolidinyl	H	H	H	H
10j	pyrrolidinyl	H	H	Cl	H
10k	pyrrolidinyl	H	H	NO_2	H

followed that entails irradiating the reaction mixture at a lower power for successive intervals of 2 min each with a cooling period of 1 min. This method is followed to avoid overheating of reactants since the unmodified household microwave oven lacks the special attributes of commercial microwave reactors in terms of control of temperature and power. This reproducible microwave protocol, however, is much simpler and cleaner when compared to conventional methods in terms of enhanced reaction rates, higher yields, and the ease of manipulation.

One-pot synthesis of 2-morpholinoisoflav-3-ene, **10a**, is thus achieved by irradiating the mixture of **5** and **6a** for 2 min in a microwave oven followed by the reaction of in situ generated **7a** with salicylaldehyde **8a** in the presence of a catalytic amount of ammonium acetate using pulsed microwave irradiation. The reaction is monitored on TLC using hexane/EtOAc (9:1, v/v) as the solvent system and the integrity of the product confirmed by the spectral data obtained. The appearance of two singlets, accounting for one proton each, at δ 5.74 (2-H) and 7.04 (4-H) in its ^{1}H NMR spectrum and its ^{13}C NMR data are in agreement with the assigned structure. Finally, the observance of molecular ion peak at *m*/*z* 293.1418 (11.2%) confirms the structure as **10a**. The other isoflavenes (Table 1) are similarly prepared, and their structures are confirmed by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectral data.

The formation of the products **10a**−**k** is supported by the mechanism delineated in Scheme 4, which is guided by the neighboring group participation of the phenolic hydroxyl function in salicylaldehyde, **8a**, followed by the dehydration of the ensuing intermediate **9a**, a process facilitated by the aryl moiety at position 3.

In conclusion, we have shown that the 2-amino-substituted isoflav-3-enes can be expeditiously prepared in a one-pot solvent-free operation using microwaves via the in situ generation of enamines and their subsequent

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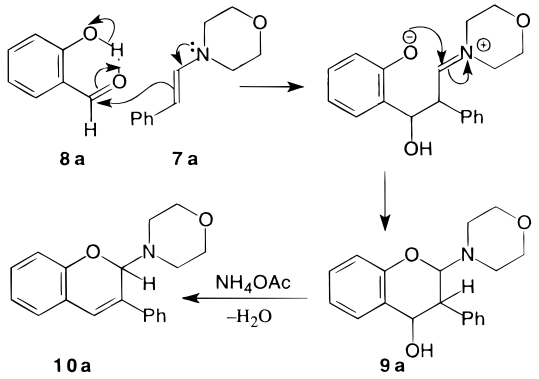
Scheme 4



reactions with salicylaldehydes. This environmentally friendly procedure does not require azeotropic removal of water using large excess of aromatic hydrocarbon solvents for the generation of enamines or the activation of the catalyst.

Experimental Section

General. All reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis Inc. and were used as received. A simple household microwave (MW) oven (900 W) equipped with a turntable was used for microwave heating. An alumina bath (neutral alumina: 125 g, mesh ~150, Aldrich; bath: 5.7 cm diameter) was used as a heat sink inside the MW oven to irradiate the reaction mixtures. TLC was performed on silica gel plates supplied by Analtech, Inc., using hexane/EtOAc (9:1, v/v) as the solvent system. Basic alumina (~150 mesh, 58 Å, surface area 155 m^2/g) supplied by Aldrich Chemical Co. was used for purification of the products. Melting points were determined on a hot-stage apparatus using 51 K/J digital thermometer and are uncorrected. All NMR spectra were recorded in deuteriochloroform ($CDCl_3$) on a spectrometer operating at 300 MHz (^1H NMR) and 75.4 MHz (^{13}C NMR) using TMS as an internal standard. Coupling constants (J values) are given in Hz. The peak assignments, whereever possible, were made on the basis of multiplicity, coupling constants, DEPT, and shielding and deshielding effects of the substituents.

One-Pot Synthesis of Substituted Isoflav-3-enes. Synthesis of 2-morpholinoisoflav-3-ene, **10a**, is representative of the general procedure employed. A mixture of phenyl acetaldehyde (0.6 g, 5 mmol) and morpholine (0.48 g, 5.5 mmol) was placed in a small beaker and irradiated in an unmodified household MW oven at its full power (900 W) for 2 min. Salicylaldehyde (0.61 g, 5 mmol) and ammonium acetate (0.02 g, 0.25 mmol) were then added to the same reaction vessel, and the reaction mixture was further irradiated in the MW oven at its 50% power for 5 min using a pulse technique.[16] Upon completion of the reaction, followed by TLC, the reaction mixture was passed through a bed of basic alumina using hexane/ether (9:1, v/v) as an eluent to afford pure 2-morpholinoisoflav-3-enes **(10a)**: yield 80%; mp 103−105 °C (lit.[5a] mp 105 °C).

6-Chloro-2-morpholinoisoflav-3-ene (10b): MW irradiation for 4 min; yield 81%; mp 137−138 °C; ^1H NMR δ 2.65 (m, 2H, NCH_2), 3.02 (m, 2H, NCH_2), 3.62 (m, 4H, CH_2OCH_2), 5.77 (s, 1H, 2-H), 6.88 (d, 1H, J = 8.2, 8-H), 7.01 (s, 1H, 4-H), 7.12 (d, 1H, J = 2.7, 5-H), 7.14 (dd, 1H, J = 2.7, 8.2, 7-H), 7.32−7.44 (m, 3H, 3′-H, 4′-H, 5′-H), 7.69 (dd, 2H, J = 1.5, 8.4, 2′-H, 6′-H); ^{13}C NMR δ 47.1 (NCH_2), 67.0 (OCH_2), 90.8 (C-2), 116.2, 122.3, 122.3, 125.3, 126.1, 126.4, 128.1, 128.6, 129.2, 129.6, 137.1, 152.2; HRMS (EI) calcd for $C_{19}H_{18}ClNO_2$ [M^+] 327.1026, found 327.1022 and 329.1001.

6-Nitro-2-morpholinoisoflav-3-ene (10c): MW irradiation for 6 min; yield 82%; mp 161−163 °C; ^1H NMR δ 2.66 (m, 2H, NCH_2), 3.02 (m, 2H, NCH_2), 3.63 (m, 4H, CH_2OCH_2), 5.94 (s, 1H, 2-H), 6.99 (d, 1H, J = 8.7, 8-H), 7.11 (s, 1H, 4-H), 7.35−7.48 (m, 3H, 3′-H, 4′-H, 5′-H), 7.69 (dd, 2H, J = 1.8, 8.3, 2′-H, 6′-H), 8.08 (d, 1H, J = 3, 5-H), 8.09 (dd, 1H, J = 3, 8.7, 7-H); ^{13}C NMR δ 46.9 (NCH_2), 66.9 (OCH_2), 92.2 (C-2), 115.3, 120.9, 121.8, 122.8, 125.4, 126.2, 128.6, 128.7, 130.5, 136.4, 141.4, 158.9; HRMS (EI) calcd for $C_{19}H_{18}N_2O_4$ [M^+] 338.1266, found 338.1263.

8-Methoxy-2-morpholinoisoflav-3-ene (10d): MW irradiation for 4 min; yield 73%, as a gum; ^1H NMR δ 2.66 (m, 2H, NCH_2), 3.09 (m, 2H, NCH_2), 3.62 (m, 4H, CH_2OCH_2), 3.88 (s, 3H, OCH_3), 5.87 (s, 1H, 2-H), 6.79 (dd, 1H, J = 3, 9, 7-H), 6.84 (dd, 1H, J = 3, 9, 5-H), 6.88 (m, 1H, 6-H), 7.09 (s, 1H, 4-H), 7.29−7.42 (m, 3H, 3′-H, 4′-H, 5′-H), 7.72 (dd, 2H, J = 1.8, 8.7, 2′-H, 6′-H); ^{13}C NMR δ 47.1 (NCH_2), 56.1 (OCH_3), 67.1 (OCH_2), 90.7 (C-2), 112.2, 119.3, 120.4, 121.8, 123.3, 126.1, 127.8, 128.4, 128.5, 137.5, 142.6, 147.0; HRMS (EI) calcd for $C_{20}H_{21}NO_3$ [M^+] 323.1521, found 323.1525.

5,7-Dimethoxy-2-morpholinoisoflav-3-ene (10e): MW irradiation for 6 min; yield 75%, as a gum; ^1H NMR δ 2.66 (m, 2H, NCH_2), 3.08 (m, 2H, NCH_2), 3.62 (m, 4H, CH_2OCH_2), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.76 (s, 1H, 2-H), 6.07 (d, 1H, J = 3, 6-H), 6.17 (d, 1H, J = 3, 8-H), 7.22−7.40 (m, 3H, 3′-H, 4′-H, 5′-H), 7.42 (s, 1H, 4-H), 7.70 (dd, 2H, J = 1.8, 8.7, 2′-H, 6′-H); ^{13}C NMR δ 46.9 (NCH_2), 55.3 (OCH_3), 55.4 (OCH_3), 67.1 (OCH_2), 90.9 (C-2), 91.4, 92.2, 104.5, 117.8, 123.3, 125.7, 127.0, 128.4, 138.1, 155.6, 156.6, 161.6; HRMS (EI) calcd for $C_{21}H_{23}NO_4$ [M^+] 353.1627, found 353.1632.

2-Piperidinoisoflav-3-ene (10f): MW irradiation for 5 min; yield 72%, as a gum; ^1H NMR δ 1.49 (m, 6H, $CH_2CH_2CH_2$), 2.62 (m, 2H, NCH_2), 3.04 (m, 2H, NCH_2), 5.78 (s, 1H, 2-H), 6.89−6.96 (m, 2H, 6-H, 8-H), 7.07 (s, 1H, 4-H), 7.14−7.22 (m, 2H, Ar-H), 7.32−7.41 (m, 3H, Ar-H), 7.74 (dd, 2H, J = 1.8, 7.2, 2′-H, 6′-H); ^{13}C NMR δ 24.6 (CH_2), 26.2 (CH_2), 47.9 (NCH_2), 91.7 (C-2), 114.8, 120.3, 121.4, 123.2, 126.3, 127.0, 127.5, 128.4, 129.2, 129.4, 138.1, 154.1; HRMS (EI) calcd for $C_{20}H_{21}NO$ [M^+] 291.1623, found 291.1627.

6-Chloro-2-piperidinoisoflav-3-ene (10g): MW irradiation for 4 min; yield 88%; mp 128−129 °C; ^1H NMR δ 1.49 (m, 6H, $CH_2CH_2CH_2$), 2.61 (m, 2H, NCH_2), 3.01 (m, 2H, NCH_2), 5.77 (s, 1H, 2-H), 6.87 (d, 1H, J = 9, 8-H), 6.98 (s, 1H, 4-H), 7.12 (d, 1H, J = 2.8, 5-H), 7.13 (dd, 1H, J = 2.8, 9.0, 7-H), 7.32−7.42 (m, 3H, 3′-H, 4′-H, 5′-H), 7.72 (dd, 2H, J = 1.9, 8.1, 2′-H, 6′-H); ^{13}C NMR δ 24.5 (CH_2), 26.1 (CH_2), 47.9 (NCH_2), 91.9 (C-2), 116.1, 122.0, 122.6, 124.9, 126.3, 127.9, 128.1, 128.4, 128.9, 130.4, 137.6, 152.6; HRMS (EI) calcd for $C_{20}H_{20}ClNO$ [M^+] 325.1233, found 325.1229 and 327.1198.

6-Nitro-2-piperidinoisoflav-3-ene (10h): MW irradiation for 2 min; yield 85%, mp 137−138 °C; ^1H NMR δ 1.49 (m, 6H, $CH_2CH_2CH_2$), 2.61 (bs, 2H, NCH_2), 3.01 (bs, 2H, NCH_2), 5.93 (s, 1H, 2-H), 6.96 (d, 1H, J = 8.1, 8-H), 7.07 (s, 1H, 4-H), 7.32−7.44 (m, 3H, 3′-H, 4′-H, 5′-H), 7.70 (dd, 2H, J = 1.8, 8.7, 2′-H, 6′-H), 8.07 (d, 1H, J = 2.7, 5-H), 8.08 (dd, 1H, J = 2.7, 8.1, 7-H); ^{13}C NMR δ 24.4 (CH_2), 26.0 (CH_2), 47.8 (NCH_2), 93.4 (C-2), 115.2, 121.1, 121.6, 122.8, 125.2, 126.4, 128.4, 128.6, 131.3, 136.8, 141.1, 159.4; HRMS (EI) calcd for $C_{20}H_{20}N_2O_3$ [M^+] 336.1474, found 336.1464.

2-Pyrrolidinoisoflav-3-ene (10i): MW irradiation for 4 min; yield 71%, as a gum; ^1H NMR δ 1.71 (m, 4H, CH_2CH_2), 2.84 (m, 2H, NCH_2), 3.14 (m, 2H, NCH_2), 6.07 (s, 1H, 2-H), 6.88−6.96 (m, 2H, 6-H, 8-H), 7.00 (s, 1H, 4-H), 7.15−7.23 (m, 2H, Ar−H), 7.32−7.44 (m, 3H, Ar−H), 7.70 (dd, 2H, J = 1.5, 8.1, 2′-H, 6′-H); ^{13}C NMR δ 24.4 (CH_2), 46.3 (NCH_2), 87.1 (C-2), 114.8, 120.3, 121.5, 122.0, 125.0, 127.9, 127.6, 128.5, 129.2, 130.5, 138.0, 154.4; HRMS (EI) calcd for $C_{19}H_{19}NO$ [M^+] 277.1466, found 277.1458.

6-Chloro-2-pyrrolidinoisoflav-3-ene (10j): MW irradiation for 2 min; yield 79%, as a gum; ^1H NMR δ 1.72 (m, 4H, CH_2-CH_2), 2.79 (m, 2H, NCH_2), 3.06 (m, 2H, NCH_2), 6.08 (s, 1H, 2-H), 6.88 (d, 1H, J = 9.0, 8-H), 6.92 (s, 1H, 4-H), 7.14 (dd, 1H, J = 2.7, 9.0, 7-H), 7.15 (d, 1H, J = 2.7, 5-H), 7.32−7.46 (m, 3H, 3′-H, 4′-H, 5′-H), 7.69 (dd, 2H, J = 1.8, 8.4, 2′-H, 6′-H); ^{13}C NMR δ 24.5 (CH_2), 46.3 (NCH_2), 87.4 (C-2), 116.2, 120.9, 122.8, 125.9, 126.1, 126.5, 128.0, 128.6, 128.8, 131.7, 137.5, 152.9; HRMS (EI) calcd for $C_{19}H_{18}ClNO$ [M^+] 311.1077, found 311.1072 and 313.1047.

6-Nitro-2-pyrrolidinoisoflav-3-ene (10k): MW irradiation for 2.5 min; yield 83%; mp 126−127 °C; ^1H NMR δ 1.72 (m, 4H, CH_2CH_2), 2.88 (bs, 4H, NCH_2), 6.22 (s, 1H, 2-H), 6.95 (d, 1H, J = 9.0, 8-H), 6.99 (s, 1H, 4-H), 7.32−7.44 (m, 3H, 3′-H, 4′-H, 5′-

(16) The reaction mixture is irradiated in a microwave oven for successive intervals of 2 min with a cooling of 1 min after every irradiation to avoid overheating of reactants.

H), 7.64 (dd, 2H, J = 1.8, 8.4, 2′-H, 6′-H), 8.07 (dd, 1H, J = 2.7, 9.0, 7-H), 8.08 (d, 1H, J = 2.7, 5-H); ^{13}C NMR δ 24.4 (CH_2), 46.2 (NCH_2), 89.2 (C-2), 115.1, 120.4, 121.1, 122.8, 125.1, 126.1, 128.4, 128.7, 132.5, 136.7, 141.0, 159.8; HRMS (EI) calcd for $C_{19}H_{18}N_2O_3$ [M^+] 322.1317, found 322.1310.

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Supporting Information Available: NMR spectra of **10b**−**k** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS: see any current masthead page for ordering information.

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