Addition of Azoles and Amines to Unsymmetrical Fumaric Esters

Paula Zaderenko,[†] M. Carmen López,[‡] and Paloma Ballesteros*,[†]

Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, c/ Senda del Rey s/n, 28040-Madrid, Spain, and Departamento de Química Inorgánica, Orgánica y Bioquímica, E. U. Politécnica de Almadén, Universidad de Castilla-La Mancha, Almadén, Ciudad Real, Spain

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The regioselectivity of nucleophilic addition of azoles to unsymmetrical fumarates yielding the corresponding (±)-2-azol-1-ylsuccinates has been studied. The major regioisomer has been identified as the one obtained from the attack of the azole to the more congestive side of the double bond. These results have been interpreted in terms of HOMO−LUMO interactions using semiempirical AM1 molecular orbital calculations. Addition of amines as alternative heteronucleophiles has been also explored to confirm the regioselectivity. Neutral hydrolysis of the two *n*-butyl ethyl (±)-2-imidazol-1-ylsuccinate regioisomers **8a** and **8b** has shown that this hydrolysis takes place faster than with the corresponding symmetrical di-*n*-butyl (±)-2-imidazol-1-ylsuccinate, and the apparent rate of hydrolysis is independent of the size of the alcohol moiety.

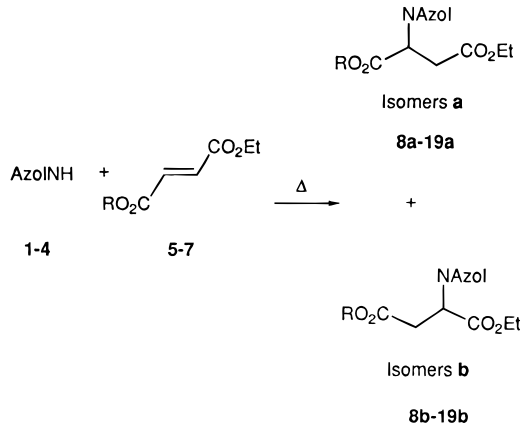
The addition reaction of imidazole and other azoles to symmetrical fumarates or maleates gave (±)-2-azol-1-ylsuccinic esters,[1−3] that underwent regioselective neutral hydrolysis to the corresponding α-half-esters: (±)-3-(alkoxycarbonyl)-2-imidazol-1-ylpropionic acids.[1,2] We established that the regioselectivity of this hydrolysis was strongly dependent on the nature of the alcohol. Thus, the rate of hydrolysis of simple esters was faster than that of esters derived from bulky alcohols.[2]

These results prompted us to combine both types of esters in the same molecule to study their behavior in the neutral hydrolysis. Taking into account the satisfactory results obtained in the addition of azoles to fumarates, we used this procedure to prepare the unsymmetrical 2-azol-1-ylsuccinic esters. No data were available in the literature on the addition of azoles or even amines to unsymmetrical fumarates or maleates. In this work we study the regioselectivity obtained in this nucleophilic addition and subsequent neutral hydrolysis of an unsymmetrical 2-imidazol-1-ylsuccinate.

Results and Discussion

The addition reactions (Scheme 1) were carried out at 100 °C under conventional heating, giving the results depicted in Table 1. Separation of isomers **a** and **b** was not possible because of their great physical similarities. However, the thermodynamic regioisomer **a**:**b** ratios could be calculated by combined GC measurements and NMR spectroscopy of the reaction mixture. Furthermore, isomers **8a** and **9a** were prepared by independent synthesis from (±)-3-(ethoxycarbonyl)-2-imidazol-1-ylpropanoic acid (**20**)[2] using a DCC esterification procedure.[4] They showed shorter GC retention times and were identified as the major isomers. Their mass spectra were identical to those assigned to **8a** and **9a** in the reaction mixture.

Scheme 1



1: Imidazole; **2**: Benzimidazole; **3**: Pyrazole;
4: 3,5-Dimethylpyrazole
5: R: *n*-Bu; **6**: R: *c*-hexyl; **7**: *tert*-Bu
8a-b: Imidazole, *n*-Bu;
9a-b: Imidazole, c-hexyl;
10a-b: Imidazole, *tert*-Bu;
11a-b: Benzimidazole, *n*-Bu;
12a-b: Benzimidazole, c-hexyl;
13a-b: Benzimidazole, *tert*-Bu
14a-b: Pyrazole, *n*-Bu;
15a-b: Pyrazole, c-hexyl;
16a-b: Pyrazole, *tert*-Bu
17a-b: 3,5-Dimethylpyrazole, *n*-Bu;
18a-b: 3,5-Dimethylpyrazole, c-hexyl;
19a-b: 3,5-Dimethylpyrazole, *tert*-Bu

Even though compounds **11a**−**19a** could not be prepared independently, their structures were differentiated from those of isomers **11b**−**19b** by their mass fragmentation patterns obtained in GC/MS analysis. Both regiosomers showed the molecular ion and were distinguished by taking into account the α-cleavage of the amino group. The presence of fragments M − CO_2R and M − CO_2Et (Table 4, supporting information) unambiguously assigns isomers **a** and **b**, respectively.

As shown in Table 1, in all cases the nucleophillic addition took place preferentially through the more sterically hindered side. This behavior was present in all azoles and more relevant in the bulkiest fumaric ester

[†] UNED.
[‡] Universidad de Castilla-La Mancha.
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(4) In all cases the dicyclohexylacylurea derivative was obtained as a side product, making the purification of the diesters difficult.

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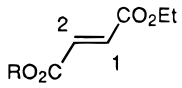
Table 1. Results Obtained in the Thermal (100 °C) Addition of Azoles to Unsymmetrical Fumaric Esters

azole	fumarate	time (h)	conversn[a] (%)	isomers **a**[b] (%)	isomers **b**[b] (%)
1	**5**	8	78[c]	50	50
1	**6**	10	78	61	39
1	**7**	7	64[d]	79	21
2	**5**	8	73[e]	52	48
2	**6**	10	75[e]	60	40
2	**7**	7[f]	44[e]	76	24
3	**5**	26	25	51	49
3	**6**	26	20	60	40
3	**7**	10	27	80	20
4	**5**	26	55	51	49
4	**6**	26	42	58	42
4	**7**	26	45	74	26

[a] Calculated from ^{1}H NMR spectra. [b] Calculated from GC chromatogram. [c] Microwave heating (400 W) gave 73% of conversion (52% of isomer **a** and 48% of isomer **b**). [d] Microwave heating (300 W) gave 41% of conversion (75% of isomer **a** and 25% of isomer **b**). [e] Reaction temperature: 120°C. [f] Longer reaction times produced unknown decomposition products.

Table 2. Charges (eV) and Orbital Coefficients for the LUMO of Fumarates Calculated by AM1



R	ΔH_f[a]	charge C1	charge C2	ϵ[b]	LUMO C1	LUMO C2
Et	−165.5	−0.112	−0.112	−0.92	0.552	−0.552
n-Bu	−179.1	−0.113	−0.112	−0.92	0.552	−0.552
c-hexyl	−178.0	−0.112	−0.112	−0.85	0.550	−0.554
t-Bu	−170.4	−0.116	−0.113	−0.82	0.549	−0.557

[a] In kcal/mol. [b] Orbital energy (eV).

7. Alternatively, and considering our previous results,[2] microwave heating was used in some cases to find out if this methodology could alter the regioisomer ratio. However, the same ratio as with conventional heating was obtained in all cases.

This regioselectivity cannot be simply explained in terms of electronic charges, since the differences in electronic charge between carbons 1 and 2 of the double bond are not significant. Therefore, other factors must be considered. Regioselectivity of nucleophilic addition to α,β-unsaturated carbonyl compounds has been explained previously in terms of HOMO−LUMO interactions.[5−8] Indeed, the values for orbital coefficients for the LUMO of carbons 2 of fumaric esters **5**−**7** (Table 2) justified the results. Thus, the bulkiest side of compound **7**, which showed the highest value LUMO coefficient, yielded the highest degree of regioselectivity.

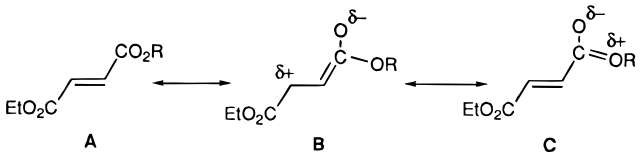
The unsymmetrical coefficients can be interpreted using valence bond structures as shown in Scheme 2. The contribution of resonance form C induces a lower LUMO coefficient in carbon 1 and consequently a higher LUMO coefficient in carbon 2. This feature is more relevant in those esters in which R is bulky, i.e., *tert*-butyl > c-hexyl > *n*-butyl. Moreover, formation of isomers **a** would release the steric congestion around carbon 2, and sp2 → sp3 rehybridation of the olefinic carbon would be encouraged.

Table 3. Results Obtained in the Thermal Addition of Amines to Unsymmetrical Fumaric Esters

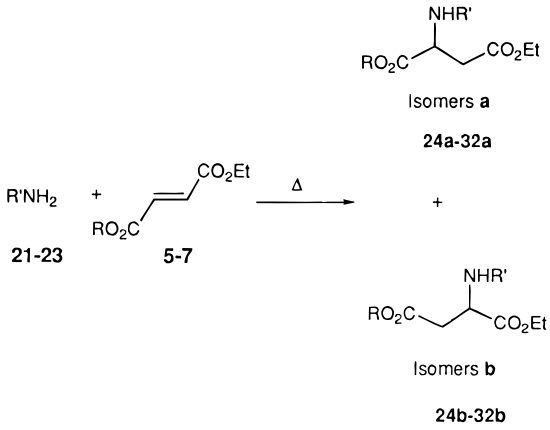
amine	fumarate	T °C	time (h)	conversn[a] (%)	isomer **a**[b] (%)	isomer **b**[b] (%)
21	**5**	25	2	83	52	48
21	**6**	25	2	61	63	37
21	**7**	25	3	73	73	27
22	**5**	25	25	90	56[c]	44
22	**6**	25	25	87	65[c]	35
22	**7**	25	25	84	77[c]	22
23	**5**	50	7.5	89	59	41
23	**6**	50	9	83	64	36
23	**7**	50	7.5	81	75	25

[a] Calculated from ^{1}H NMR spectra. [b] Calculated from the GC chromatogram. [c] Two diastereomers were identified.

Scheme 2



Scheme 3



21: R' = *n*-Bu; **22**: R' = 2-Bu; **23**: R' = c-hexyl
24a-b: R = *n*-Bu, R' = *n*-Bu
25a-b: R = c-hexyl, R' = *n*-Bu;
26a-b: R = *tert*-Bu, R' = *n*-Bu;
27a-b: R = *n*-Bu, R' = 2-Bu;
28a-b: R = c-hexyl, R' = 2-Bu;
29a-b: R = *tert*-Bu, R' = 2-Bu
30a-b: R = *n*-Bu, R' = c-hexyl,
31a-b: R = c-hexyl, R' = c-hexyl
32a-b: R = *tert*-Bu, R' = c-hexyl

Taken together, these results indicate that the regioselectivity depends exclusively on the fumaric ester double bond, being independent of the nature of the azole. To confirm this, we used other nitrogen nucleophiles such as *n*-butylamine (**21**), (±)-2-butylamine (**22**), and cyclohexylamine (**23**) instead of azole and we obtained the corresponding (alkylamino)succinic esters **24a**−**32a** and **24b**−**32b** (Scheme 3). Only primary amines were reactive enough to be used as models; *tert*-butyl amine and secondary amines gave only traces of the desired adduct. Again, the same regioselectivity observed with azoles was present in these cases (Table 3).

Both regioisomers **a** and **b** were difficult to separate. As in the case of azole derivatives, regioisomers were identified by their mass fragmentation pattern. Although compounds **23a**−**29a** and **23b**−**29b** did not show the molecular ion, the base peak corresponded to a typical

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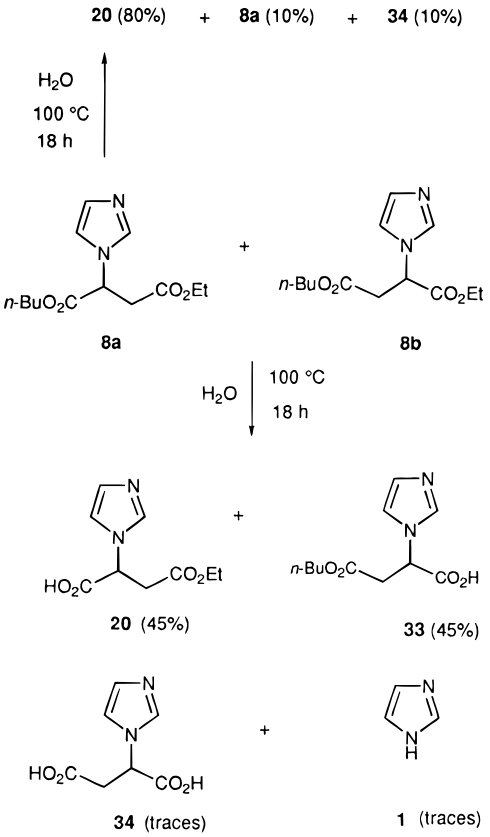
Scheme 4



homolytic cleavage of α bonds to an amino group. Regioisomers **a** and **b** were easily recognized by the fragments M − CO_2R and M − CO_2Et, respectively (Table 5, supporting information).

Finally, we have investigated the neutral hydrolysis of isolated compound **8a** and of the mixture of regioisomers **8a** and **8b** with the aim to compare their behavior with the previously studied 2-imidazol-1-ylsuccinates (Scheme 4). Considering that in di-*n*-butyl 2-imidazol-1-ylsuccinate the acetate-type ester hydrolyzed nearly three times slower than the corresponding diethyl ester (100 °C/48 h vs 18 h),[2] a slower hydrolysis in **8a** with respect to **8b** should be expected. Using this methodology, it should be easy to separate **8a** from **8b**, because the monoester and the diester present very different physical properties.[2] Thus, a mixture (1:1) of **8a** and **8b** was hydrolyzed as described previously for the diethyl ester. Surprisingly, the ^{1}H NMR spectrum in DMSO-d_6 of the reaction crude showed the absence of the starting diesters and the corresponding half esters: **20** and (±)-3-(butoxycarbonyl)-2-imidazol-1-ylpropanoic acid (**33**) (1:1) were the major products. Some traces of imidazole and (±)-2-imidazol-1-ylsuccinic acid (**34**) were observed. Furthermore, hydrolysis of isolated **8a** in the same conditions yielded the half ester **20** (80%) as shown the ^{1}H NMR spectrum in D_2O of the reaction mixture.

These results suggest that the $B_{AC}3$ mechanism previously proposed for this hydrolysis,[2] on the basis of analogies with other esters activated with electron-withdrawing substituents,[9−11] may depend on several factors. The independence of the concentration shown in the hydrolysis of the diethyl ester[2] suggested an intramolecular mechanism in which the imidazole was involved. However, present results would indicate that intermolecular interactions, probably related with the translational diffusion of this molecules and water, must be taken into account to fully explain the influence of both alcohol moieties.[12]

Experimental Section

General Procedures. A description of some analytical instruments, spectral data formats, and standard calibration have been previously published.[2] GC/MS spectra were recorded on a Shimadzu QP-5000 at 70 eV. Phase columm (30 m): nonpolar poly(dimethylsiloxane); variable column temperature from 150 to 250 °C. Products were purchased from commercial sources. The following compounds were prepared according to literature procedures: (±)-3-(ethoxycarbonyl)-2-imidazol-1-ylpropanoic acid (**20**),[2] *tert*-butyl ethyl fumarate (**7**).[13]

Preparation of Unsymmetrical Fumarates 5 and 6 by Esterification of Monoethyl Fumarate. The following fumarates were prepared according to a slightly modification of the literature procedure described for **7**. A one-necked flask, equipped with a calcium chloride drying tube, was charged with monoethyl fumarate (0.2 mol), dry CH_2Cl_2 (200 mL), the corresponding alcohol (0.60 mol), and 4-DMAP (0.16 mol). The solution was stirred and cooled in an ice bath to 0°C while DCC (0.22 mol) was added over a 5-min period. The solution was allowed to stir at this temperature for 5 min more, and then the ice bath was removed and the mixture was stirred at room temperature for 2 h. After the precipitated dicyclohexylurea was filtered, the Cl_2CH_2 was evaporated *in vacuo* and the residue purified over a silica gel column using hexane: ethyl acetate, 95:5, as chromatographic eluent to obtain compounds **5** and **6** as colorless oils that were distilled under reduced pressure.

***n*-Butyl ethyl fumarate (5):** $bp_{0.01}$ 54−56 °C; yield 67%; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.2 Hz), 0.90−1.45 (m, 2H),1.31 (t, 3H, J = 7.2 Hz), 1.62−1.69 (m, 2H), 4.21 (q, 2H, J = 7.1 Hz), 4.26 (t, 2H, J = 7.1 Hz), 6.84 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.0 (q), 13.5 (q), 18.6 (t), 30.1(t), 60.6 (t), 64.5 (t), 133.0 (d), 133.1 (d), 164.1 (s), 164.2 (s); MS m/z 155 (26, M − OCH_2CH_3), 56 (100); IR (film) ν 1710 (CO) cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.96; H, 8.06. Found: C, 60.20; H, 7.91.

Cyclohexyl ethyl fumarate (6): $bp_{0.01}$ 73−74 °C; yield 66%; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.2 Hz), 1.37−1.87 (m, 10H), 4.22 (q, 2H, J = 7.2 Hz), 4.80−4.90 (m, 1H), 6.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 23.3 (t), 24.9 (t), 31.1(t), 60.8 (t), 73.2 (d), 133.8 (d), 132.9 (d), 163.9 (s), 164.6 (s); MS m/z 181 (12, M − OCH_2CH_3), 67 (100), 55 (95); IR (film) ν 1700 (CO) cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.60; H, 7.79.

***tert*-Butyl ethyl fumarate (7):** $bp_{0.01}$ 42−44 °C (lit.[10] bp_{12} 105−107 °C); yield 60%; ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 27.7 (q), 60.9 (d), 81.5 (s), 132.4 (d), 135.3 (d), 163.8 (s), 164.8 (s); MS m/z 155 (6, M − OCH_2CH_3), 57 (100); IR (film) ν 1710 (CO) cm^{-1}.

Addition of Azoles 1−4 to Unsymmetrical Fumarates 5−7. General Procedures. Method a. A mixture of azole (2.5 mmol) and the corresponding fumarate (2.5 mmol) was heated in an oil bath at 100 °C (120 °C for benzimidazole) and the time shown in Table 1 for each compound. The ^{1}H NMR spectra and GC chromatograms of the mixtures are included as supporting information. **Method b.** A mixture of azole (2.5 mmol) and the corresponding fumaric esters (2.5 mmol) was located in a 23 mL PARR bomb with a Teflon sample cup. The reaction mixture was heated in the microwave oven at 300 W for 3 min. After being cooled at room temperature, the bomb

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was placed into an ice bath and carefully opened. The crude reaction mixture was analyzed by ^{1}H NMR spectroscopy.

Preparation of Unsymmetrical 2-Imidazol-1-ylsuccinic Esters 8a and 9a by Esterification of 20. To an ice-cooled suspension of DCC (21.8 or 10.2 mmol) and DMAP (1.5 or 0.8 mmol) in CH_2Cl_2 (20 or 10 mL) and *n*-butanol (52.6 mmol) or cyclohexanol (28.8 mmol) was slowly added **20** (17.8 or 9.4 mmol). The mixture was stirred at room temperature for 2 h. The white powder of *N*,*N*′-dicyclohexylurea was filtered off and the organic solution concentrated *in vacuo*. The residue was purified by column chromatography over a silica gel column using ethyl acetate as eluent to obtain **8a** or **9a** as colorless oils.

(±)-1-*n*-Butyl 4-ethyl 2-imidazol-1-ylsuccinate (8a): $bp_{0.01}$ 135 °C; yield 42% after distillation; picrate mp 99−102 °C (from ethanol); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7.1 Hz, CH_3), 1.21 (t, 3 H, J = 7.1 Hz, CH_3), 1.18−1.38 (m, 2 H, CH_2), 1.50−1.65 (m, 2 H, CH_2), 3.08 (AB part, 2 H, J_{AB} = 16.7 Hz, J_{AX} = 7.7 Hz, J_{BX} = 6.8 Hz, CH_2), 4.13 (q, 2 H, J = 7.1 Hz, OCH_2), 4.15 (t, 2 H, J = 6.5 Hz, OCH_2), 5.21 (X part, 1 H, CH), 6.97 (t, 1 H, J = 1.1 Hz, H5), 7.06 (t, 1 H, J = 1.1 Hz, H4), 7.56 (t, 1 H, J = 1.1 Hz, H2); ^{13}C NMR ($CDCl_3$) δ 13.2 (q), 13.7 (q), 18.6 (t), 30.0 (t), 37.2 (t), 55.6 (d), 61.1(t), 66.0 (t), 117.7 (d), 129.4 (d), 136.8 (d), 168.2 (s), 168.9 (s); MS *m*/*z* 241 (4, M − 28), 95 (100); IR (film) ν 1720 (CO) cm^{-1}. Anal. Calcd for $C_{19}H_{23}N_5O_{11}$ (picrate): C, 45.87; H, 4.66; N, 14.08. Found: C, 46.24; H, 4.55; N, 13.71.

(±)-1-Cyclohexyl 4-ethyl 2-imidazol-1-ylsuccinate (9a): yield 75% from column chromatography; picrate mp 117−119 °C (from ethanol); ^{1}H NMR ($CDCl_3$) δ 1.2−1.9 (m, 10 H, c-hexyl-H), 1.21 (t, 3 H, J = 7.2 Hz, CH_3), 3.08 (AB part, 2 H, J_{AB} = 17.7 Hz, J_{AX} = 7.6 Hz, J_{BX} = 6.8 Hz, CH_2), 4.12 (q, 2 H, J = 7.2 Hz, OCH_2), 4.75−4.90 (m, 1 H, c-hexyl-H1), 5.19 (X part, 1 H, CH), 6.98 (bs, 1 H, H5), 7.26 (bs, 1 H, H4), 7.57 (bs, 1 H, H2); ^{13}C NMR ($CDCl_3$) δ 13.5 (q), 22.7 (t), 22.8 (t), 24.6 (t), 30.5 (t), 30.6 (t), 27.0 (t), 55.5 (d), 60.8 (t), 74.3 (d), 117.5 (d), 129.0 (d), 136.7 (d), 167.3 (s), 168.8 (s); MS *m*/*z* 294 (11, M^+), 95 (100); IR (film) ν 1730 (CO) cm^{-1}. Anal. Calcd for $C_{21}H_{25}N_5O_{11}$ (picrate): C, 48.18; H, 4.81; N, 13.38. Found: C, 48.53; H, 4.95; N, 13.42.

Addition of Amines 21−23 to Unsymmetrical Fumarates 5−7. General Procedure. A mixture of amine (2.5 mmol) and fumarate (2.5 mmol) was heated at the temperature and the time shown in Table 4 (supporting information) for each compound. The ^{1}H NMR spectra and GC chromatograms of the mixtures are included as supporting information.

Neutral Hydrolysis of Compounds 8a and 8b. A 1 M solution of a 1:1 mixture of **8a** and **8b** or isolated **8a** in distilled water was heated in an oil bath at 100 °C for 18 h. Then, the reaction mixture was concentrated *in vacuo* and the residue analyzed by ^{1}H NMR in D_2O or DMSO-d_6.

Molecular Orbital Calculations. Semiempirical MO calculations were carried out using the AM1 method[14] as implemented in the Hyperchem (version 4.0, 1994) and MOPAC (version 6.0, 1990) programs. Geometries were optimized using the Polak-Ribieri conjugate gradient method (RMS gradient 0.05 kcal mol^{-1} Å^{-1}).

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Supporting Information Available: ^{1}H NMR ($CDCl_3$) spectra and GC chromatograms of the reaction crudes of the addition of azoles **1**−**4** to fumarates **5**−**7**. ^{1}H NMR ($CDCl_3$) spectra and GC chromatograms of the reaction crudes of the addition of amines **21**−**23** to fumarates **5**−**7**. Selected mass fragmentations of esters **8a**−**19a**, **8b**−**19b**, **24a**−**32a**, and **24b**−**32b** (Tables 4 and 5) (44 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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