[4 + 2]Cycloaddition of Monocyclic Imidazole Derivatives with Electron-deficient Acetylenes

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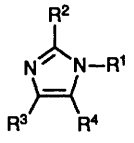
1-Alkylidene- and 1-arylmethylene-amino-4-aryl-2-mercapto-1*H*-imidazole derivatives **2–11** react with dimethyl acetylenedicarboxylate (DMAD) in hot chlorobenzene to give the corresponding retro-Diels–Alder products 1-alkylidene- and 1-arylmethylene-amino-2-mercapto-1*H*-pyrrole-3,4-dicarboxylate derivatives **19–26** and benzonitriles **27** in high yield. No intermediate Diels–Alder adducts could be isolated from these substrates. 1-Amino-2-methylthio-4-phenyl-1*H*-imidazole **1** gives dimethyl 1-[1,2-bis(methoxycarbonyl)vinylamino]-2-methylthio-4-phenyl-1*H*-1,3-diazepine-5,6-dicarboxylate **28** in addition to dimethyl 1-amino-2-methylthio-1*H*-pyrrole-3,4-dicarboxylate **18**, with the ratio **18**:**28** ranging from 2:1 to 3:1 under the same reaction conditions. At lower temperature, however, the former cycloadduct is obtained as the sole product in acetonitrile. No cycloaddition to these imidazole derivatives is observed with ethyl propiolate or with bis(trimethylsilyl)acetylene even under forced conditions. Any changes in the substituents or their positions on the imidazoles **2–11** that otherwise successfully give rise to the cycloaddition decidedly inhibited the reaction. Among a number of di- and tri-substituted imidazole derivatives employed as substrates, only a limited number bearing an amino or alkylidene- or arylmethylene-amino, a substituted mercapto, and an aryl group at the 1-, 2- and 4-position, respectively, can produce the corresponding pyrroledicarboxylates through the retro-Diels–Alder reaction.

In the course of our studies on the cyclization of amino-imidazoles to obtain new ring systems, it was found that 1-amino-2-methylthio-4-phenyl-1*H*-imidazole **1** gave a 1:2 cyclo-adduct, dimethyl 1-[1,2-bis(methoxycarbonyl)vinylamino]-2-methylthio-4-phenyl-1*H*-1,3-diazepine-5,6-dicarboxylate **28** and a retro-Diels–Alder product **18** rather than the expected imidazopyridazine derivative upon treatment with DMAD. [4 + 2]Cycloaddition of monocyclic imidazole derivatives † has not been investigated as extensively as in the case of their oxygen analogues, oxazoles.[2] As in furan, the strongly electronegative oxygen in the oxazole ring may poorly contribute to the aromaticity of the five-membered ring so that the remaining two double bonds might behave as a 1,3-diene system. Although a few reports[3] concerning treatment of an imidazole derivative with a dienophile have been published, none of these papers describe 1,4-cycloaddition across the imidazole ring. Thus we now report the [4 + 2]cycloaddition of certain imidazole derivatives and the effect of the substitution pattern and the nature of the substitutents on the substrate on the cycloaddition across the imidazole ring.

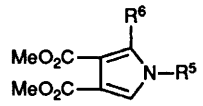


Compd.	R^1	R^2	R^3	R^4
1	NH_2	SMe	Ph	H
2	MeCH=N	SMe	Ph	H
3	PhCH=N	SMe	Ph	H
4	PhCH=N	SMe	4-$MeOC_6H_4$	H
5	PhCH=N	SMe	4-$O_2NC_6H_4$	H
6	4-$MeOC_6H_4CH$=N	SMe	Ph	H
7	4-$MeOC_6H_4CH$=N	$SCH_2CH{=}CH_2$	Ph	H
8	4-$MeOC_6H_4CH$=N	SCH_2Ph	Ph	H
9	2,6-$Cl_2C_6H_3CH$=N	SMe	Ph	H
10	PhCH=N	SCD_3	Ph	H
11	Ph(Me)C=N	SMe	Ph	H
12	PhCH=N	SMe	H	Ph
13	4-$MeOC_6H_4CH$=N	SMe	Me	H
14	AcNH	SMe	Ph	H
15	PhCH=N	NH_2	Ph	H
16	PhCH=N	NHAc	Ph	H
17	Ac	H	Ph	H

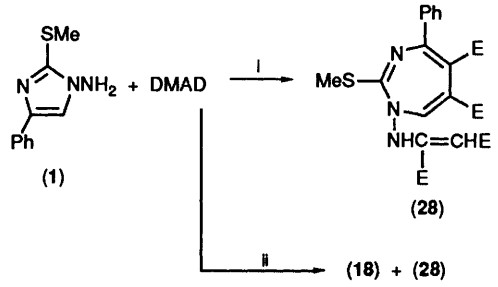
Results and Discussion

The cycloaddition reaction of 1-amino-2-methylthio-4-phenyl-1*H*-imidazole **1** was performed by heating the imidazole **1** and a slight excess of DMAD in acetonitrile at 80 °C (Scheme 1). Chromatographic separation gave a 1:2 cycloadduct **28** and no 1:1 adduct **30** or **31** was found in the reaction mixture, regardless of the ratio of aminoimidazole **1** to DMAD employed. The maximum yield (45%) of cycloadduct **28** was obtained when the molar ratio of DMAD to imidazole was 2:1. On the other hand, when the aminoimidazole was heated with a slight excess of DMAD at a higher temperature (145–150 °C) in chlorobenzene, a retro-Diels–Alder product dimethyl 1-amino-2-methylthio-1*H*-pyrrole-3,4-dicarboxylate **18** was produced in addition to the diazepine **28**, with the ratio **18**:**28** ranging from 2:1 to 3:1. A probable Michael adduct **29** could not be detected in the reaction mixture. The first step of this reaction at higher temperature may thus be 1,4-cycloaddition to form an intermediate 1:1 cycloadduct **30** rather than nucleophilic addition of the amino group to the triple bond of DMAD to form an enamine **31**. The cycloadduct **30** should then rapidly lose a nitrile **27** to produce the pyrrole product **18**. At lower

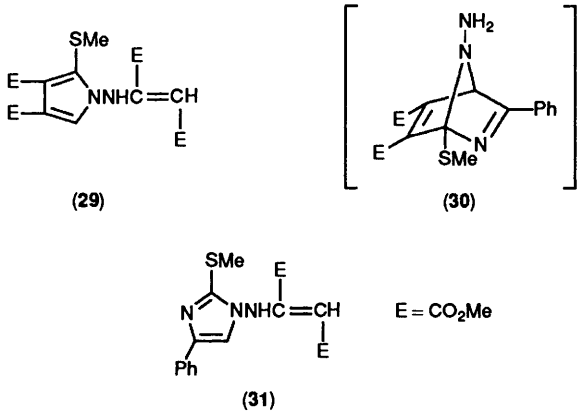
† The 1,4-cycloaddition of DMAD across a condensed imidazole ring was suggested by Abe *et al.*,[1] in their work on imidazo[2,1-*b*]thiazole systems.



Compd.	R^5	R^6
18	NH_2	SMe
19	MeCH=N	SMe
20	PhCH=N	SMe
21	PhCH=N	SCD_3
22	4-$MeOC_6H_4CH$=N	SMe
23	4-$MeOC_6H_4CH$=N	$SCH_2CH{=}CH_2$
24	4-$MeOC_6H_4CH$=N	SCH_2Ph
25	2,6-$Cl_2C_6H_3CH$=N	SMe
26	Ph(Me)C=N	SMe
27	R^3CN	

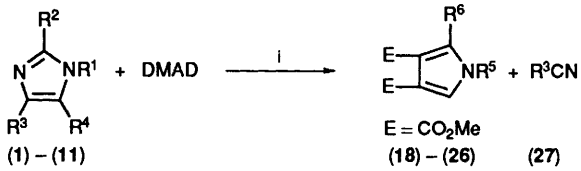


Scheme 1. *Conditions:* i, 80 °C, MeCN; ii, 145–150 °C, PhCl. E = CO_2Me.



temperatures, however, [2 + 2]cycloaddition to the 4,5-bond of the imidazole **1** followed by ring expansion as reported by Troxler *et al.*[3b] with nucleophilic addition of the amino group can predominate to form 1,3-diazepine-5,6-dicarboxylate **28** probably due to kinetic control. [2 + 2]Cycloaddition involving the 2,3-bond is unlikely to occur because compound **28** exhibits the NMR signal for the phenyl group as a singlet (δ_H 7.39), suggesting vicinal substitution.[4] Compound **28** was highly stable thermally and remained intact after exposure of its solution in chlorobenzene to temperatures of 145–150 °C (bath temperature) for 4 h. To assist structural elucidation, reduction of compound **28** with zinc dust in acetic acid or catalytic hydrogenation was attempted; however, these gave a complex mixture and no information on the structure.

1-Alkylideneamino- and 1-arylmethyleneamino-imidazole derivatives **2–11** successfully gave the corresponding pyrroledicarboxylates **19–26** upon treating with DMAD in chlorobenzene at 145–150 °C (Scheme 2).



Scheme 2. *Conditions:* i, 145–150 °C, PhCl.

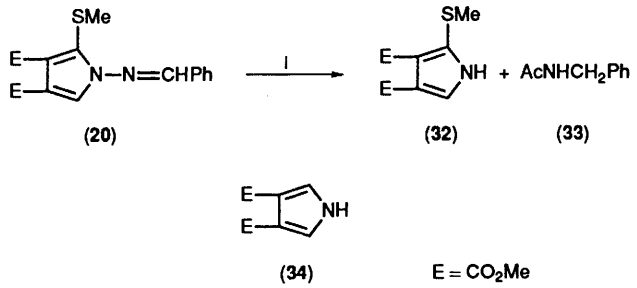
The driving force of the conversion of an imidazole into a pyrrole derivative through the retro-Diels–Alder reaction might be the formation of two aromatic molecules, a pyrrole derivative stabilized by the dicarboxylate structure and an aromatic nitrile. Comparison of imidazoles **3** and **6** with the 5-phenyl isomer **12** and the 4-methyl analogue **13**, respectively, which are unreactive to cycloaddition with DMAD, leads to the conclusion that conjugation is an essential factor between the substituent at the 4-position and N(3) in the imidazole ring for the present [4 + 2]cycloaddition. As expected, introduction of an electron-withdrawing group into the substituent R^3 on the imidazole **3** significantly retarded the rate of reaction and lowered the yield of the corresponding pyrrole **20**. Similarly, acetylation of aminoimidazole **1** to form compound **14** resulted in complete inhibition of the reactivity of the aminoimidazole as a diene. Use of an electron-rich alkyne, such as bis(trimethylsilyl)acetylene or methyl propiolate, in place of DMAD resulted in the total recovery of the imidazole **3**. These observations suggest that the reactions of 1,2,4-trisubstituted imidazoles **1–11** with DMAD may be LUMO (dienophile)–HOMO (diene) controlled.

A further structural requirement that makes it possible to bring about the 1,4-cycloaddition of imidazoles with DMAD may be the presence of a sulphur atom bonded to the 2-position. None of imidazoles **15**, **16** and **17**, which lack a sulphur-containing group at the 2-position, gave the corresponding pyrrole derivatives; instead, reaction resulted in either a highly darkened mixture containing unchanged starting imidazole **16** or formation of tar [**15** and **17**]. It seems that the effect of the sulphur atom on the pyrrole formation through 1,4-cycloaddition with DMAD may be steric rather than electronic. The bulky sulphur atom should serve to push out the nitrile **27** from the highly crowded transition state, thereby leaving the corresponding pyrroledicarboxylate.

The resonances of the four ring carbons in the 1-aminopyrrole **18** appeared at δ_C 111.77 as a doublet ($^2J_{CH}$ 5.4 Hz), δ_C 121.21 as a doublet ($^3J_{CH}$ 6.1 Hz), δ_C 126.97 as a multiplet, and δ_C 128.29 as a doublet ($^1J_{CH}$ 194.6 Hz) and could easily be assigned to C-4, C-3, C-2 and C-5, respectively. Because trideuteriomethylthio compound **21** showed the C-2 resonance* (δ_C 127.24) as a doublet with $^3J_{CH}$ 6.6 Hz, the three-bond coupling along the pyrrole ring in the pyrroledicarboxylates might generally have a coupling constant ~6 Hz. The assignment of the resonances for C-3 and C-4 of the pyrrole ring could thus be made on the basis of the magnitude of their coupling constant with the proton at the 5-position. The resonances of the four ring carbons of other pyrroles **19–26** ranged from δ_C 113.28–114.79 for C-4, δ_C 117.82–123.10 for C-5, δ_C 121.28–123.43 for C-3 and δ_C 124.07–128.72 for C-2, with large coupling constants ($^1J_{CH}$ 192–194 Hz) being observed for the C-5 doublets.

An attempt to convert compound **20** into the known dimethyl pyrrole-3,4-dicarboxylate **34**[5] by reductive cleavage gave instead dimethyl 2-methylthio-1*H*-pyrrole-3,4-dicarboxylate **32** and *N*-benzylacetamide **33** (Scheme 3).

* The resonance of C-2 of this compound could unambiguously be assigned by its exceptionally weak intensity.



Scheme 3. *Reagents:* i, Zn, AcOH, Ac_2O.

Experimental

Microanalyses were performed with a Perkin-Elmer 240D elemental analyser at the Microanalytical Laboratory of Kitasato University. IR, UV and mass spectra were recorded on Perkin-Elmer 983, JASCO UVIDEC 610 and JMS-DX100 instruments, respectively. ^1H and ^{13}C NMR spectra were obtained with a JNM-FX90Q spectrometer operating at 89.55 and 22.50 MHz, respectively. Preparative high-pressure liquid chromatography (HPLC) was carried out on a Kusano Kagaku KHLC-201 instrument with a 300 × 22 or a 300 × 15 mm glass column packed with silica gel.

Di- and Tri-substituted Imidazoles.—Most of the imidazoles employed are known compounds and were prepared according to the literature method.[6] New compounds are as follows:

Compound **11** (20%), pale yellow prisms, m.p. 105–106 °C [from benzene–hexane (1:4)] (Found: C, 70.15; H, 5.6; N, 13.6. $C_{18}H_{17}N_3S$ requires C, 70.3; H, 5.6; N, 13.7%); δ_H 2.33 (3 H, s, CMe), 2.60 (3 H, s, SMe), 7.24 (1 H, s, 5-H), 7.40 (6 H, m, ArH) and 7.82 (4 H, m, ArH); *m/z* 307 (M^+, 67%), 189 (46) and 118 (100). Compounds **2** and **9** were obtained by an alternative procedure as follows.

Preparation of 1-*Ethylideneamino*-2-*methylthio*-4-*phenyl*-1H-*imidazole* **2**.—A mixture of 1-amino-2-methylthio-4-phenyl-1*H*-imidazole **1** (1.0 g, 4.9 mmol), 90% acetaldehyde (10 ml, 0.18 mol) and ethanol (5 ml) was heated at 50 °C for 3 h and evaporated. The residual oil was subjected to column chromatography on silica gel (Wakogel C-300, 50 g) with benzene–ethanol (98:2 v/v) as eluant. Fractions containing the desired imidazole were collected and evaporated to give the imidazole as an oil (0.67 g, 59%) which gradually crystallized upon storage. Recrystallization from hexane gave the *title compound* **2** as needles, m.p. 77–78 °C (Found: C, 62.4; H, 5.6; N, 18.1. $C_{12}H_{13}N_3S$ requires C, 62.3; H, 5.7; N, 18.2%); $\delta_H(CDCl_3)$ 2.18 (3 H, d, *J* 5.4 Hz, =CH*Me*), 2.71 (3 H, s, SMe), 7.33 (3 H, m, ArH), 7.53 (1 H, s, 5-H), 7.76 (2 H, m, ArH) and 7.78 (1 H, q, *J* 5.4 Hz, =C*H*Me); *m/z* 231 (M^+, 100%) and 189 (71).

1-(2,6-*Dichlorobenzylideneamino*)-2-*methylthio*-4-*phenyl*-1H-*imidazole* **9**.—This was prepared when a mixture of 2,6-dichlorobenzaldehyde (0.4 g, 2.3 mmol), 1-amino-2-methylthio-4-phenyl-1*H*-imidazole (0.4 g, 2.0 mmol), acetic acid (0.1 ml) and benzene–ethanol (1:1 v/v, 10 ml) was heated under reflux for 24 h. The desired *imidazole* (**9**) crystallized out of the hot reaction mixture as analytically pure, fluorescent yellow prisms (0.53 g, 71%), m.p. 172–173 °C (Found: C, 56.4; H, 3.6; N, 11.5. $C_{17}H_{13}Cl_2N_3S$ requires C, 56.4; H, 3.6; N, 11.6%); $\delta_H(CDCl_3)$ 2.71 (3 H, s, SMe), 7.35 (6 H, m, $Cl_2C_6H_3$ and ArH), 7.74 (1 H, s, 5-H), 7.83 (2 H, m, ArH) and 8.51 (1 H, s, N=CH); *m/z* 363 (M^+ + 2, 27%), 361 (M^+, 37), 253 (29) and 189 (100).

Imidazoles **14** and **16** were obtained by acetylation of the corresponding aminoimidazoles **1** and **15**,[7] respectively.

Compound **14** (55%) was obtained as fibre-like crystals, m.p. 157–159 °C (from benzene) (Found: C, 58.4; H, 5.3; N, 17.15. $C_{12}H_{13}N_3OS$ requires C, 58.3; H, 5.3; N, 17.0%); ν_{max}(KBr) 3176 (NH) and 1712 cm^{-1} (C=O); $\delta_H[(CD_3)_2SO]$ 2.10 (3 H, s, COMe), 2.64 (3 H, s, SMe), 7.26 (1 H, s, 5-H), 7.29 (3 H, m, ArH), 7.76 (2 H, m, ArH) and 8.47 (1 H, br s, NH); *m/z* 247 (M^+, 100%) and 189 (22).

Compound **16** (75%) was obtained as yellow needles, m.p. 167–169 °C (from benzene) (Found: C, 71.1; H, 5.4; N, 18.2. $C_{18}H_{16}N_4O$ requires C, 71.0; H, 5.3; N, 18.4%); ν_{max}(KBr) 3391 (NH) and 1704 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.61 (3 H, s, Me), 7.55 (7 H, m, ArH and 5-H), 7.84 (4 H, m, ArH), 8.20 (1 H, br s, NH) and 8.26 (1 H, s, N=CH); *m/z* 304 (M^+, 91%), 262 (32) and 158 (100).

Deuteriation of the Aminoimidazole **1**.—A solution of the imidazole **1** (1.0 g) in MeOD (5 ml) was boiled under argon with protection from atmospheric moisture for 1 h and was then evaporated. The residue was again subjected to this procedure to achieve *ca.* 100% deuteriation. The product 1-(*N*,*N*-dideuterioamino)-2-methylthio-4-phenyl-1*H*-imidazole (**1**; $R^1 = ND_2$) thus obtained was immediately used for the preparation of the monodeuteriated derivative of compound **28**.

The Reaction of Imidazoles with DMAD.—Formation of dimethyl 1-*benzylideneamino*-2-*methylthiopyrrole*-3,4-*dicarboxylate* **20** (*general procedure for conversion of imidazoles into pyrroledicarboxylates through retro-Diels–Alder reaction*). A mixture of 1-benzylideneamino-2-methylthio-4-phenyl-1*H*-imidazole **3** (0.29 g, 1 mmol), DMAD (0.17 g, 1.2 mmol) and chlorobenzene (5 ml) was heated at 140–145 °C (bath temperature) for 6 h. An additional amount of DMAD (0.04 g, total amount 1.5 mmol) was added and the mixture was heated for a further period of 4 h. After evaporation of the solvent under reduced pressure, the residue was subjected to preparative HPLC on silica gel with chloroform–dichloromethane (2:1 v/v) as eluant. Further chromatographic purification of the impure compound thus obtained on silica gel with dichloromethane–hexane (1:1 v/v) gave the desired *product* **20** (0.29 g, 87%) as needles, m.p. 105 °C [from benzene–hexane (9:1 v/v)] (Found: C, 57.8; H, 4.7; N, 8.3. $C_{16}H_{16}N_2O_4S$ requires C, 57.8; H, 4.85; N, 8.4%); λ_{max}(EtOH) 215, 260 and 309 nm (ε 23 080, 19 200 and 21 700 dm^3 mol^{-1} cm^{-1}); $\nu_{max}(CCl_4)$ 1732 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.44 (3 H, s, SMe), 3.83 (3 H, s, OMe), 3.93 (3 H, s, OMe), 7.54 (3 H, m, ArH), 7.74 (1 H, s, 5-H), 7.87 (2 H, m, ArH) and 8.50 (1 H, s, N=CH); $\delta_C(CDCl_3)$ 19.60 (q, $^1J_{CH}$ 141.3 Hz, SMe), 51.49 (q, $^1J_{CH}$ 146.8 Hz, OMe), 52.08 (q, $^1J_{CH}$ 146.8 Hz, OMe), 114.33 (d, $^2J_{CH}$ 5.0 Hz, C-4), 118.47 (d, $^1J_{CH}$ 193.0 Hz, C-5), 122.00 (d, $^3J_{CH}$ 6.6 Hz, C-3), 127.36 (m, C-2), 128.70, 129.07, 132.14 and 132.60 (Ph), 155.49 (dt, $^1J_{CH}$ 161.6, $^3J_{CH}$ 4.9 Hz, N=CH), 163.11 (dq, $^3J_{CH}$ 3.8, $^4J_{CH}$ 1.6 Hz, 3-CO_2) and 165.04 (dq, $^3J_{CH}$ 3.8 and 1.6 Hz, 4-CO_2); *m/z* 332 (M^+, 94%), 301 (32), (196 (58) and 118 (100).

This compound was also obtained by similar treatment of imidazoles **4** and **5** with DMAD in 75 and 47% yield, respectively. Trideuterio analogue **21** was similarly prepared from the corresponding imidazole **10** which, in turn, was obtained from *S*-(trideuteriomethyl)isothiosemicarbazone[8] according to the literature method.[6] The following new pyrroles were similarly obtained.

Compound **19** (68%), prisms, m.p. 116–117 °C [from hexane–benzene (9:1)] (Found: C, 48.8; H, 5.2; N, 10.3. $C_{11}H_{14}N_2O_4S$ requires C, 48.9; H, 5.2; N, 10.4%); λ_{max}(EtOH) 208 and 246 nm (ε 20 300 and 16 400 dm^3 mol^{-1} cm^{-1}); $\nu_{max}(CCl_4)$ 1732 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.24 (3 H, d, *J* 5.4 Hz, CH*Me*), 2.37 (3 H, s, SMe), 3.79 (3 H, s, OMe), 3.90 (3 H, s, OMe), 7.53 (1 H, s, 5-H) and 8.01 (1 H, q, *J* 5.4 Hz, C*H*Me); $\delta_C(CDCl_3)$ 18.94 (dq, $^1J_{CH}$ 129.2, $^2J_{CH}$ 9 Hz, CH*Me*), 19.67 (q, $^1J_{CH}$ 140.8 Hz, SMe), 51.51

(q, $^1J_{CH}$ 146.8 Hz, OMe), 52.15 (q, $^1J_{CH}$ 147.3 Hz, OMe), 113.55 (d, $^2J_{CH}$ 4.9 Hz, C-4), 118.99 (d, $^1J_{CH}$ 192.4 Hz, C-5), 121.60 (d, $^3J_{CH}$ 6.0 Hz, C-3), 125.89 (m, C-2), 159.03 (dq, $^1J_{CH}$ 161.1, $^2J_{CH}$ 7.7 Hz, *C*HMe), 163.11 (dq, $^3J_{CH}$ 3.8, $^4J_{CH}$ 1.6 Hz, 3-*C*O_2Me), and 165.13 (dq, $^3J_{CH}$ 3.8 and 1.6 Hz, 4-*C*O_2Me); *m/z* 270 (M^+, 100%), 239 (33), 223 (39) and 196 (37).

Compound **22** (81%), light yellow needles, m.p. 98 °C [from benzene–hexane (1:1)] (Found: C, 56.4; H, 5.1; N, 7.8. $C_{17}H_{18}N_2O_5S$ requires C, 56.35; H, 5.0; N, 7.7%); λ_{max}(EtOH) 205, 227, 276sh and 323 nm (ε 18 800, 19 400, 14 000 and 26 200 dm^3 mol^{-1} cm^{-1}); ν_{max}(CCl_4) 1 733 cm^{-1} (C=O); δ_H($CDCl_3$) 2.43 (3 H, s, SMe), 3.82 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.92 (3 H, s, OMe), 6.98 (2 H, d, *J* 8.8 Hz, ArH), 7.69 (1 H, s, 5-H), 7.80 (2 H, d, *J* 8.8 Hz, ArH) and 8.42 (1 H, s, N=CH); δ_C($CDCl_3$) 19.52 (q, $^1J_{CH}$ 140.8 Hz, SMe), 51.42 (q, $^1J_{CH}$ 146.8 Hz, OMe), 52.00 (q, $^1J_{CH}$ 146.8 Hz, OMe), 55.52 (q, $^1J_{CH}$ 144.6 Hz, OMe), 114.04 (d, $^3J_{CH}$ 4.9 Hz, C-4), 114.77, 125.28, 130.55 and 163.21 (aryl), 118.87 (d, $^1J_{CH}$ 192.4 Hz, C-5), 121.82 (d, $^3J_{CH}$ 6.0 Hz, C-3), 126.90 (q, $^3J_{CH}$ 7.1 Hz, C-2), 155.93 (dt, $^1J_{CH}$ 160.5, $^3J_{CH}$ 4.9 Hz, N=CH), 163.21 (dq, $^3J_{CH}$ 3.8, $^4J_{CH}$ 1.6 Hz, 3-*C*O_2Me), and 165.11 (dq, $^3J_{CH}$ 3.8 and 1.6 Hz, 4-*C*O_2Me); *m/z* 362 (M^+, 100%), 331 (14), 196 (18) and 148 (48).

Compound **23** (87%), light yellow needles, m.p. 96 °C [from benzene–hexane (1:1)] (Found: C, 58.7; H, 5.2; N, 7.2. $C_{19}H_{20}N_2O_5S$ requires C, 58.8; H, 5.2; N, 7.2%); λ_{max}(EtOH) 202, 225, 276sh and 323 nm (ε 28 000, 27 500, 19 300 and 31 500 dm^3 mol^{-1} cm^{-1}); ν_{max}(CCl_4) 1732 cm^{-1} (C=O); δ_H($CDCl_3$) 3.49 (2 H, d, *J* 7.1 Hz, SCH_2), 3.82 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.92 (3 H, s, OMe), 4.86 and 5.01 (each 1 H, m, together =CH_2), 5.60–5.98 (1 H, m, CH_2CH=), 7.02 (2 H, d, *J* 8.8 Hz, ArH), 7.68 (1 H, s, 5-H), 7.85 (2 H, d, *J* 8.8 Hz, ArH) and 8.42 (1 H, s, N=CH); δ_C($CDCl_3$) 39.39 (t,* $^1J_{CH}$ 142.9 Hz, SCH_2), 51.54 (t, $^1J_{CH}$ 146.8 Hz, OMe), 52.13 (t, $^1J_{CH}$ 146.8 Hz, OMe), 55.49 (t, $^1J_{CH}$ 144.6 Hz, OMe), 113.64 (d, $^2J_{CH}$ 4.9 Hz, C-4), 117.77 (t,* $^1J_{CH}$ 156.3 Hz, =CH_2), 118.77 (d, $^1J_{CH}$ 192.4 Hz, C-5), 123.21 (d, $^3J_{CH}$ 6.0 Hz, C-3), 124.58 (m, C-2), 133.60 (d,*$^1J_{CH}$ 154.5 Hz, CH_2CH=), 114.62, 125.07, 130.50 and 163.15 (aryl), 155.71 (dt, $^1J_{CH}$ 160.0, $^3J_{CH}$ 4.9 Hz, N=CH), 163.01 (dq, $^3J_{CH}$ 4.0, $^4J_{CH}$ 1.6 Hz, 3-*C*O_2Me), and 165.11 (dq, $^3J_{CH}$ 4.4 and 1.6 Hz, 4-*C*O_2Me); *m/z* 388 (M^+, 16%), 356 (23), 214 (19), 174 (100) and 134 (39).

Compound **24** (86%), needles, m.p. 109–110 °C [from benzene–hexane (1:9)] (Found: C, 62.8; H, 5.0; N, 6.4. $C_{23}H_{22}N_2O_5S$ requires C, 63.0; H, 5.1; N, 6.4%); λ_{max}(EtOH) 204, 223, 275 and 320 nm (ε 27 800, 27 200, 16 400 and 23 800 dm^3 mol^{-1} cm^{-1}); ν_{max}(CCl_4) 1730 cm^{-1} (C=O); δ_H($CDCl_3$) 3.80 (3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 4.00 (2 H, s, SCH_2), 6.96 (2 H, d, *J* 8.9 Hz, *p*-MeOC_6H_4), 7.08 (5 H, s, Ph), 7.56 (1 H, s, 5-H), 7.67 (2 H, d, *J* 8.9 Hz, *p*-MeOC_6H_4), and 8.08 (1 H, s, N=CH); δ_C($CDCl_3$) 41.34 (t, $^1J_{CH}$ 142.9 Hz, SCH_2), 51.54 (q, $^1J_{CH}$ 146.8 Hz, OMe), 52.15 (q, $^1J_{CH}$ 146.8 Hz, OMe), 55.49 (q, $^1J_{CH}$ 144.0 Hz, OMe), 113.62 (d, $^2J_{CH}$ 4.9 Hz, C-4), 119.06 (d, $^1J_{CH}$ 192.4 Hz, C-5), 123.43 (d, $^3J_{CH}$ 5.5 Hz C-3), 124.28 (m, C-2), 114.47, 125.01, 130.55, and 162.94 (MeOC_6H_4), 127.09, 128.23, 128.94 and 137.49 (Ph), 156.08 (dt, $^1J_{CH}$ 160.5, $^3J_{CH}$ 4.4 Hz, N=CH), 162.94 (dq, $^3J_{CH}$ 4.2, $^4J_{CH}$ 1.1 Hz, 3-*C*O_2Me) and 165.13 (dq, $^3J_{CH}$ 3.8 and 1.1 Hz, 4-*C*O_2Me); *m/z* 438 (M^+, 4%), 224 (95) and 91 (100).

Compound **25** (95%), prisms, m.p. 124–125 °C (from benzene) (Found: C, 47.9; H, 3.5; N, 7.0. $C_{16}H_{14}Cl_2N_2O_4S$ requires C, 47.9; H, 3.5; N, 7.0%); λ_{max}(EtOH) 205, 218, 259 and 289 nm (ε 25 600, 27 200, 16 000 and 12 800 dm^3 mol^{-1} cm^{-1}); ν_{max}(CCl_4) 1734 cm^{-1} (C=O); δ_H($CDCl_3$) 2.44 (3 H, s, SMe), 3.84 (3 H, s, OMe), 3.93 (3 H, s, OMe), 7.40 (3 H, m, ArH), 7.81 (1 H, s, 5-H) and 8.81 (1 H, s, N=CH); δ_C($CDCl_3$) 19.77 (q, $^1J_{CH}$ 141.3 Hz, SMe), 51.71 (q, $^1J_{CH}$ 146.8 Hz, OMe), 52.29 (q, $^1J_{CH}$ 146.8 Hz, OMe), 114.79 (d, $^2J_{CH}$ 4.4 Hz, C-4), 117.82 (d, $^1J_{CH}$ 193.5 Hz, C-5), 122.43 (d, $^3J_{CH}$ 6.0 Hz, C-3), 128.72 (m, C-2), 127.87, 129.21, 131.65 and 135.60 (aryl), 150.29 (d, $^1J_{CH}$ 168.2, N=CH), 162.98 (dq, $^3J_{CH}$ 3.8, $^4J_{CH}$ 1.1 Hz, 3-*C*O_2Me) and 164.93 (dq, $^3J_{CH}$ 3.8 and 1.1 Hz, 4-*C*O_2Me); *m/z* 402 (M^+ + 2, 61%), 400 (M^+, 100), 365 (45), 333 (86) and 166 (34).

Compound **26** (75%), light yellow plates, m.p. 132–134 °C [from benzene–hexane (1:9)] (Found: C, 59.0; H, 5.2; N, 8.0. $C_{17}H_{18}N_2O_4S$ requires C, 58.95; H, 5.2; N, 8.1%); λ_{max}(EtOH) 212 and 252 nm (ε 25 200 and 23 500 dm^3 mol^{-1} cm^{-1}); ν_{max}(CCl_4) 1730 cm^{-1} (C=O); δ_H($CDCl_3$) 2.24 (3 H, s, CMe), 2.30 (3 H, s, SMe), 3.80 (3 H, s, OMe), 3.92 (3 H, s, OMe), 7.25 (1 H, s, 5-H), 7.52 (3 H, m, Ph) and 7.95 (2 H, m, Ph); δ_C($CDCl_3$) 16.94 (q, $^1J_{CH}$ 129.8 Hz, C*Me*), 19.42 (q, $^1J_{CH}$ 141.3 Hz, SMe), 51.47 (q, $^1J_{CH}$ 146.3 Hz, OMe), 52.17 (q, $^1J_{CH}$ 146.8 Hz, OMe), 113.28 (d, $^2J_{CH}$ 5.5 Hz, C-4), 121.28 (d, $^3J_{CH}$ 6.0 Hz, C-3), 123.10 (d, $^1J_{CH}$ 194.1 Hz, C-5), 124.07 (m, C-2), 127.58, 128.79, 132.07 and 135.65 (Ph), 163.30 (dq, $^3J_{CH}$ 3.8, $^4J_{CH}$ 1.1 Hz, 3-*C*O_2Me), 165.32 (dq, $^3J_{CH}$ 3.8 and 1.0 Hz, 4-*C*O_2Me) and 176.41 (m, N=*C*Me); *m/z* 346 (M^+, 37%), 196 (10), 132(24), 118 (100) and 77 (79).

Reaction of 1-*Amino*-2-*methylthio*-4-*phenyl*-1H-*imidazole* **1** *with DMAD. Formation of* (1:2) *Cycloadduct* **28**.—1-Amino-2-methylthio-4-phenyl-1*H*-imidazole **1** (0.5 g, 2.44 mmol) was dissolved in hot acetonitrile (5 ml). To the solution was added DMAD (0.69 g, 4.88 mmol) and the mixture was heated under reflux for 4 h. The solvent was removed under reduced pressure and the residual oil was subjected to column chromatography on silica gel (Wakogel C-300, 70 g) with benzene–ethanol (98:2) as eluant. An oil (0.53 g) from the cycloadduct-rich fractions was extracted several times with hot hexane and the crystals (0.38 g, 45%) which separated out from the extracts were collected and recrystallized from benzene–hexane (1:9) to give *compound* **28** as yellow needles, m.p. 113–114 °C (Found: C, 53.85; H, 4.6; N, 8.5. $C_{22}H_{23}N_3O_8S$ requires C, 54.0; H, 4.7; N, 8.6%); λ_{max}(EtOH) 205, 228sh, 272 and 357 nm (ε 29 200, 21 000, 20 900 and 14 900 dm^3 mol^{-1} cm^{-1}); ν_{max}(CCl_4) 3236br (NH), 1742vs and 1698 cm^{-1} (C=O); δ_H($CDCl_3$) 2.50 (3 H, s, SMe), 3.22, 3.80, 3.92 and 3.98 (each 3 H, OMe), 5.42 (1 H, s, =*CH*CO_2Me), 6.79 (1 H, d,† *J* 0.77 Hz, 7-H), 7.39 (5 H, s, Ph) and 11.28 (1 H, br s, NH); δ_C($CDCl_3$) 19.17 (q, $^1J_{CH}$ 142.4 Hz, SMe), 51.30 (q, $^1J_{CH}$ 146.2 Hz, OMe), 52.17 (q, $^1J_{CH}$ 147.9 Hz, OMe), 52.39 (q, $^1J_{CH}$ 147.3 Hz, OMe), 97.12 (dd, $^1J_{CH}$ 169.9, $^3J_{CH}$ 2.2 Hz, =*C*HCO_2Me), 105.78 (dd, $^1J_{CH}$ 185.8, $^3J_{CH}$ 2.2 Hz, C-7), 119.22 (s, HNC=), 127.87, 128.82, 129.31 and 135.56 (Ph), 136.04 (m, C-4), 138.09 (dq, $^3J_{CH}$ 4.9, $^4J_{CH}$ 1.6 Hz, C-2), 142.44 (s, C-6), 145.36 (s, C-5), 161.67 (q, $^3J_{CH}$ 3.8 Hz, 5-*C*O_2Me), 162.84 (q, $^3J_{CH}$ 3.8 Hz, =CH*C*O_2Me), 164.30 (dq, $^3J_{CH}$ 4.4 and 3.8 Hz, NHC*C*O_2Me) and 167.89 (q, $^3J_{CH}$ 3.8 Hz, 6-*C*O_2Me); *m/z* 489 (M^+, 36%), 259 (47), 246 (100), 227 (56), 118 (27) and 103 (37).

Deuteriated analogues of the aminoimidazole **1** at the amino moiety or the 5-position were similarly treated with DMAD to give the corresponding deuteriated cycloadducts, which served to assist us in our assignment of the ^1H and ^{13}C NMR spectra of compound **28**. The monodeuteriated compound‡ on the ethylenic carbon of the fumarate moiety obtained from 1-(*N*,*N*-dideuterio)amino-2-methylthio-4-phenyl-1*H*-imidazole (**1**; R^1 = ND_2) lacked the δ_H 5.42 and δ_C 97.12 resonances. On the other hand, the 7-deuteriocycloadduct was produced from the 5-deuteriated derivative of aminoimidazole (**1**; R^4 = D) and showed no δ_H 6.79 or δ_C 105.78 resonances. It also showed a simple quartet for C-2 at δ_C 138.09 ($^3J_{CH}$ 4.9 Hz).

* Each component splits into a multiplet.

† Irradiation of the NH signal (at irradiation frequency 54.8802 kHz) changed the doublet into a sharp singlet.

‡ This compound showed the NH band (3235 cm^{-1}) rather than the expected ND band due to hydrogen exchange during work-up. Its C–D stretching band appeared at 2309 cm^{-1}.

Formation of Dimethyl 1-*Amino*-2-*methylthio*-1H-*pyrrole*-3,4-*dicarboxylate* **18**.—When the above reaction was performed at 145–150 °C in chlorobenzene, starting with the 1-aminoimidazole **1** (0.21 g, 1 mmol) and DMAD (0.21 g, 1.5 mmol), followed by work-up according to the general procedure, the pyrrole **18** was prepared as a light yellow oil (0.13 g, 53%); λ_{max}(EtOH) 212 and 259 nm (ε 19 900 and 7 200 dm^3 mol^{-1} cm^{-1}); $\nu_{max}(CCl_4)$ 3354, 3295 and 3225 (NH_2) and 1722 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.37 (3 H, s, SMe), 3.78 and 3.89 (each 3 H, s, OMe) and 7.41 (1 H, s, 5-H); $\delta_C(CDCl_3)$ 20.23 (q, $^1J_{CH}$ 141.3 Hz, SMe), 51.44 (q, $^1J_{CH}$ 146.8 Hz, OMe), 52.13 (q, $^1J_{CH}$ 147.3 Hz, OMe), 111.77 (d, $^2J_{CH}$ 5.5 Hz, C-4), 121.21 (d, $^3J_{CH}$ 6.0 Hz, C-3), 126.97 (m, C-2), 128.29 (d, $^1J_{CH}$ 194.6 Hz, C-5), 163.37 (dq, $^3J_{CH}$ 3.8, $^4J_{CH}$ 1.1 Hz, 3-CO_2Me) and 165.32 (dq, $^3J_{CH}$ 3.8 and 1.6 Hz, 4-CO_2Me). This product **18** was identified by its reaction with anisaldehyde to convert it into the *p*-methoxybenzylidene derivative **22**. In this reaction, cycloadduct **28** (0.08 g, 16%) was also isolated from a fraction preceding that of the first pyrrole.

Reductive Cleavage of Dimethyl 1-*Benzylideneamino*-2-*methylthio*-1H-*pyrrole*-3,4-*dicarboxylate* **20**.—A mixture of the pyrrole **20** (0.1 g), zinc dust (3.0 g), acetic acid (10 ml) and acetic anhydride (4 ml) was stirred at room temperature for 2 h, and then evaporated under reduced pressure. The residue was extracted with chloroform (10 ml) and the extract was washed with 5% aq. sodium carbonate. After evaporation of the solvent, the residue was subject to preparative HPLC on silica gel with chloroform as eluant to give a homogeneous fraction containing dimethyl 2-methylthio-1*H*-pyrrole-3,4-dicarboxylate **32**. Recrystallization from benzene gave the pyrrole **32** (46 mg, 67%) as prisms, m.p. 91–92 °C (Found: C, 47.3; H, 4.85; N, 6.05. $C_9H_{11}NO_4S$ requires C, 47.15; H, 4.8; N, 6.1%); $\nu_{max}(CCl_4)$ 3459 (free) and 3287br (bonded) (NH) and 1730 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.43 (3 H, s, SMe), 3.80 (3 H, s, OMe), 3.89 (3 H, s, OMe), 7.31 (1 H, d, *J* 3.1 Hz, 5-H) and 9.04 (1 H, br, NH);* *m/z* 229 (M^+, 45%), 198 (52), 197 (100) and 166 (78).

* Decoupling of the NH resonance at an irradiation frequency of 54.6818 kHz gave the 5-H signal as a singlet at δ_H 7.31.

References

1 N. Abe, T. Nishiwaki and N. Komoto, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 3308.

2 R. Grigg, R. Hayes and J. L. Jackson, *Chem. Commun.*, 1969, 1167; R. Grigg and J. L. Jackson, *J. Chem. Soc. C*, 1970, 552; S. R. Ohlsen and S. Turner, *J. Chem. Soc. C*, 1971, 1632; J. J. K. Novak, *Collect. Czech. Chem. Commun.*, 1975, **40**, 2855; T. Jaworski and T. Mizerski, *Rocz. Chem.*, 1976, **50**, 359.

3 (*a*) T. Novinson, D. E. O'Brien and R. K. Robins, *J. Heterocycl. Chem.*, 1974, **11**, 873; (*b*) F. Troxler, H. P. Weber, A. Jaunin and H. R. Loosli, *Helv. Chim. Acta*, 1974, **57**, 750; (*c*) H. P. Weber, J. J. Petcher, A. Jaunin, and F. Troxler, *Helv. Chim. Acta*, 1975, **58**, 552.

4 L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, 1966, **31**, 1878.

5 R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1961, 457.

6 C. Yamazaki, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1846.

7 H. Beyer, A. Hetzheim, H. Honeck, D. Ling and T. Pyl, *Chem. Ber.*, 1968, **101**, 3151.

8 C. Yamazaki, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1767.

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