On the Reaction of 3,5-Dimethylpyrazole with Acetylenic Esters†

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Addition of 3,5-dimethylpyrazole (**1**) to the triple bond of dimethyl acetylenedicarboxylate (DMAD) is highly stereoselective in aprotic solvents, yielding almost exclusively the *supra*-addition product (**2**-*E*). In protic solvents, the reaction is less stereoselective, giving as the major product the *antara*-addition adduct (**2**-*Z*). Addition of (**1**) to the olefinic esters (**2**-*E*) and (**2**-*Z*) yields the diastereoisomers (**3**) and (**4**), being the *supra*-addition product predominant in both protic and aprotic solvents.

Although the reaction of *N*H-pyrazoles with acetylenic esters has been widely studied by different authors, the results obtained are difficult to rationalize. Two mono- and two bis-adducts have been obtained depending on four factors: the nature of the pyrazole (pyrazole, 3,5-dimethylpyrazole, and 3,4,5-trimethylpyrazole), the nature of the acetylenic ester (dimethyl acetylenedicarboxylate, DMAD, and methyl propiolate, MP), the molar ratio of the reagents (pyrazole to acetylenic ester ratio, 1:1 and 2:1) and, finally, the nature of the solvent (ethyl ether, carbon tetrachloride, dioxane, methanol, or none). Literature results[1-6] are reported in Table 1.

Acheson *et al.*[7] carried out the reaction of indazole, benzotriazole, and various triazoles with DMAD by refluxing in acetonitrile. In all cases, after recrystallization from methanol, only a bisadduct, the stereochemistry of which was not assigned, was obtained.

In order to clarify the mechanism of this reaction (Scheme) and to make coherent the different results, we have studied the reaction of 3,5-dimethylpyrazole (**1**) with DMAD and MP under various reaction conditions (Tables 2 and 3). In all cases, the reaction mixtures have been analysed by ^{1}H n.m.r.; Tables 4 and 5 summarize the ^{1}H n.m.r. data of the products.

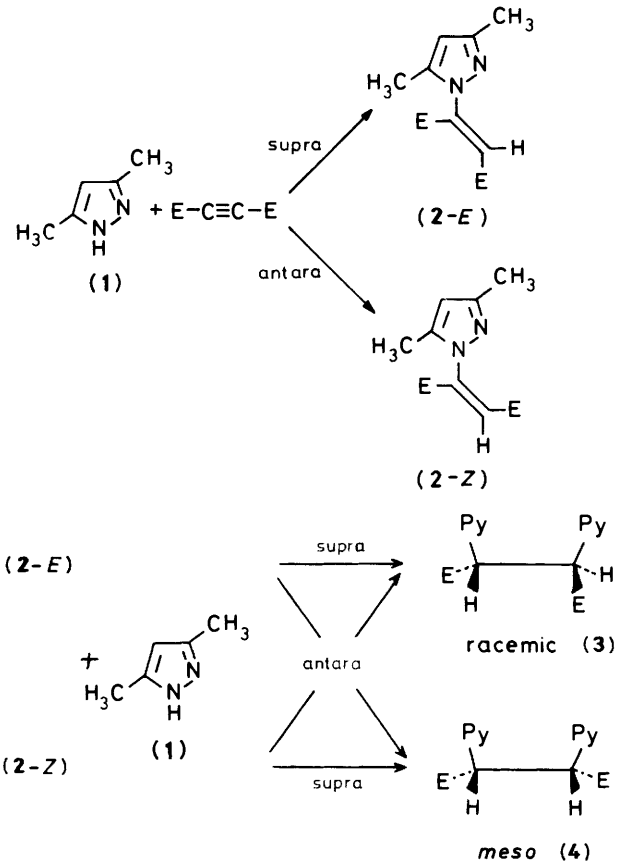
Results and Discussion

In aprotic solvents (Table 2, entries 1 and 3) using a pyrazole–DMAD ratio of 2:1, only the (**2**-*E*) isomer with a mixture of the bisadducts (**3**) and (**4**) was obtained. No (**2**-*Z*) isomer was detected (absence of the δ 7.05 signal in the ^{1}H n.m.r. spectrum of the reaction mixture). In methanol (Table 2, entry 2) both monoadducts were obtained. When, to avoid double addition to the triple bond, pyrazole–ester ratios of 1:1 and shorter reaction times were used, a mixture of monoadducts, in which the *antara*-addition isomer predominated, was obtained in methanol as solvent (Table 2, entries 4 and 5). With DMAD, 14% of a mixture of bisadducts was also obtained.

When carbon tetrachloride was used as solvent (Table 2, entry 6), the almost pure *supra*-addition isomer (**2**-*E*), with traces of bisadducts and *Z*-isomer, was obtained. Thus, in carbon tetrachloride the reaction proceeds preferentially *via supra*-addition as expected for an aprotic solvent.[4,5]

To verify whether the *meso*: racemic ratio obtained in the bisadduct mixture depends on the structure of the initial monoadduct, that is, if the addition to the double bond of the monoadduct (**2**) is stereospecific or not, we have studied (Table 3) the reaction of both monoadducts (**2**-*E*) and (**2**-*Z*) with 3,5-dimethylpyrazole (**1**). We have found that the reaction is stereoselective, the ratio of bisadducts (**3**) and (**4**) depending on the nature of the starting isomer. Although the *Z*-isomer reacts almost completely, the reactivity of the *E*-isomer is much lower, especially in methanol, and >80% of unaltered (**2**-*E*) was recovered. This difference in the reactivity of both monoadducts could be the reason why no *Z*-isomer was observed by Reimlinger[4,5] (Table 2, entries 1 and 6). It cannot be excluded, however, that the lesser stereochemical constraints of pyrazole compared with 3,5-dimethylpyrazole are responsible for Reimlinger's results.

We have established experimentally that isomerization between the *E*- and *Z*-isomers or between *meso* and racemic diastereoisomers does not occur.



Scheme. E = CO_2Me; Py = 3,5-dimethylpyrazol-1-yl

† Part of this work was presented at the ESOC III meeting, Canterbury, 1983.

Table 1. Literature results on the reaction of pyrazoles with acetylenic esters

Ref.	Pyrazole	Acetylenic ester	Molar ratio[a]	Solvent	Products
1	Parent	DMAD	1:1	Ethyl ether	Two bisadducts (m.p. 158 and 139 °C)[b]
	3,5-Me_2	DMAD	1:1	Ethyl ether	One monoadduct (m.p. 58 °C) and one bisadduct (m.p. 188 °C)
2	Parent	DMAD	2:1	Ethyl ether	One bisadduct (m.p. 158 °C)[c]
	3,5-Me_2	DMAD	1:1	Ethyl ether	One bisadduct (m.p. 188 °C)[c,d]
	3,4,5-Me_3	DMAD	2:1	Ethyl ether	One bisadduct (m.p. 193 °C)[c]
	3,4,5-Me_3	DMAD	1:1	Ethyl ether	One monoadduct (m.p. 96 °C)[e]
4	Parent	DMAD	2:1	CCl_4	One monoadduct (b.p. 117 °C at 0.2 mmHg)[f] and one bisadduct[f]
5	Parent	DMAD	2:1	Ethyl ether	Two bisadducts (m.p.s 142 and 167 °C)[g]
	Parent	MP	1:1	None	One monoadduct (m.p. 81 °C)[h]
6	Parent	MP	1:1	Dioxane	Two monoadducts (non-separated)[i]
	Parent	MP	1:1	Methanol	Two monoadducts (non-separated)[j]

[a] Pyrazole–acetylenic ester. [b] Isolated on only one occasion. [c] A succinate.[3] [d] No trace of the described[1] 1:1-adduct could be obtained. [e] Likely to be a fumarate on the basis of analogy (named fumarate in the summary and in the Experimental section). [f] The *E*-isomer (a maleate).[5] [g] The product melting at 158 °C (refs. 1 and 2) yields by recrystallization two succinates. [h] The *E*-isomer (acrylate). [i] A 3:1 mixture of *E*- and *Z*-isomers (acrylates). [j] A 27:73 mixture of *E*- and *Z*-isomers (acrylates).

Table 2. Experimental results obtained in the reaction between 3,5-dimethylpyrazole (**1**) and acetylenic esters DMAD and MP

Ester	(1):Ester	Solvent	Temp.	Time	% (2-*E*)	% (2-*Z*)	*E*:*Z*	% (3)	% (4)	racemic:*meso*
DMAD	2:1	CCl_4	Room temp.	5 d	70		100:0	16	14	53:47
DMAD	2:1	CH_3OH	Room temp.	5 d	15	30	33:67	28	27	51:49
DMAD	2:1	CH_3CN	Reflux	16 h	42		100:0	33	24	58:42
DMAD	1:1	CH_3OH	Room temp.	20 h	35	51	40:60	5	9	64:36
MP	1:1	CH_3OH	Reflux	90 h	14	42	25:75			
DMAD	1:1	CCl_4	Room temp.	20 h	97.5	2.5	97.5:2.5	Traces		

Table 3. Experimental results obtained in the reaction between 3,5-dimethylpyrazole (**1**) and the olefinic esters (**2**-*E*) and (**2**-*Z*)

					Products		
Ester	Solvent	Time	% (2-*E*)	% (2-*Z*)	% (3)	% (4)	racemic : *meso*
(2-*E*)	CCl_4	20 h	92		8	Trace	
(2-*E*)	CCl_4	5 d	82		15	3	83:17
(2-*E*)	CH_3OH	20 h	100				
(2-*E*)	CH_3OH	5 d	90		7	3	70:30
(2-*E*)	CH_3OH	14 d	73		17	10	63:37
(2-*Z*)	CCl_4	20 h		27	24	49	33:67
(2-*Z*)	CCl_4	5 d			38	62	38:62
(2-*Z*)	CH_3OH	20 h		58	15	27	36:64
(2-*Z*)	CH_3OH	5 d			48	52	48:52

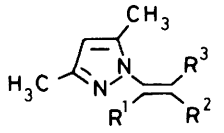
To establish the relative addition rate of 3,5-dimethylpyrazole (**1**) to the (**2**-*Z*) and (**2**-*E*) monoadducts, competitive reactions have been carried out. Equimolar mixtures of both isomers have been compelled to react with different amounts of (**1**). Because of the large reactivity difference, the *Z*-isomer disappears before the *E*-isomer begins to react. Thus, the experiment was carried out as follows: an equimolar mixture of (**2**-*E*) and (**2**-*Z*) was placed in a n.m.r. tube, and (**1**) in a 5:1 molar proportion was added. Measurements were made at fixed intervals of time. When all (**2**-*Z*) had disappeared the fraction of (**1**) consumed was added, to keep the 1:5 ratio of both isomers with regard to the pyrazole. A first-order reaction [Py = constant] was assumed. By plotting $-\ln(c/c_0)$ against time, the half-life was determined which allowed us to calculate the relative reactivity of both isomers: $k_{(2\text{-}Z)}/k_{(2\text{-}E)} = 78$.

Moreover, these experiments confirm that in carbon tetrachloride the isomer (**2**-*E*) reacts highly stereoselectively yielding the racemic bisadduct (**3**) almost exclusively, while the (**2**-*Z*) isomer yields mainly the *meso* bisadduct (**4**) with a certain proportion of (**3**) (Table 3).

Structural assignment of the bisaddition products was done by ^1H n.m.r. using Eu(TFC)$_3$\{europium tris-[3-(2,2,2-trifluoro-1-hydroxyethylidene)-D-camphorate]\}.[8] From the mixture of bisadducts one of the diastereoisomers, m.p. 186 °C, was obtained pure by successive recrystallizations from methanol. The other, m.p. 129 °C, was isolated by recrystallizing the above residue from water. The isomer of m.p. 186 °C (methanol) was identified as the *meso* diastereoisomer (*R,S*)-(**4**) because in the presence of Eu(TFC)$_3$ (Figure 1a) the n.m.r. signal of its exocyclic CH group was split into an AB system with J_{AB} 10.8 Hz showing that the main conformation around the saturated C–C bond is the one with the hydrogen atoms in an antiperiplanar position (Figure 2). The n.m.r. spectrum of the racemic diastereoisomer (*RR,SS*)-(**3**), of m.p. 129 °C (water), recorded in the presence of the same chiral reagent (Figure 1b) shows the exocyclic CH signals of both enantiomers separated as two singlets (two A_2 systems).

It can be observed (Table 5) that in the *meso* compound (**4**), higher m.p. (methanol), the exocyclic CH n.m.r. signal is more deshielded than that of the racemic one (**3**), while the OCH_3

Table 4. ^{1}H N.m.r. chemical shifts (δ values; $CDCl_3$; internal Me_4Si) of DMAD and MP adducts



			δ					
R^1	R^2	R^3	3-CH_3	4-H	5-CH_3	R^1	R^2	R^3
CO_2CH_3	CO_2CH_3	H	2.20	6.00	2.33	3.97[a] and 3.77[a]		6.17
				$J_{4,5}$ 0.8 Hz[b]				
CO_2CH_3	H	CO_2CH_3	2.20	5.93	2.12	3.82[a]	7.05	3.63[a]
				$J_{4,5}$ 0.8 Hz[b]				
H	H	CO_2CH_3	2.18	5.85	2.22	6.73	5.53	3.75
				$J_{4,5}$ 0.8 Hz[b]		J_{R^1,R^2} 10.0 Hz		
H	CO_2CH_3	H	2.25	5.95	2.33	7.82	3.77	6.38
						J_{R^1,R^3} 14.0 Hz		

[a] These values can be interchanged. [b] This coupling with the methyl in position 5 is characteristic of a pyrazole 4-H.[9] This assignment is coherent with the results obtained with the chiral lanthanide shift reagent.

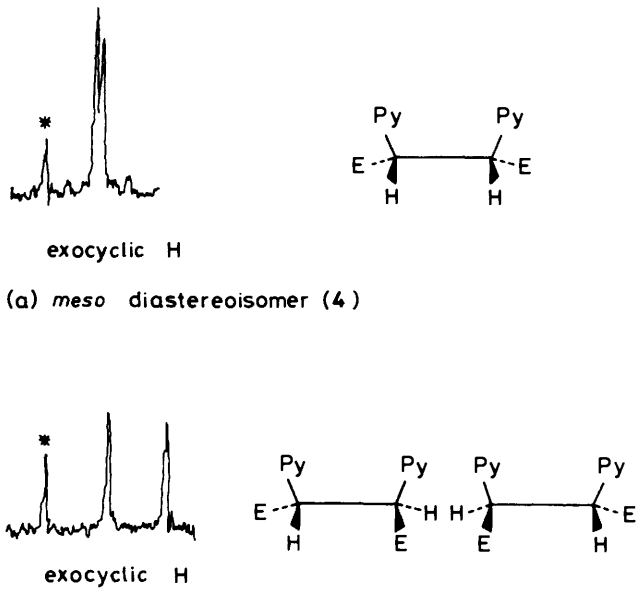


Figure 1.

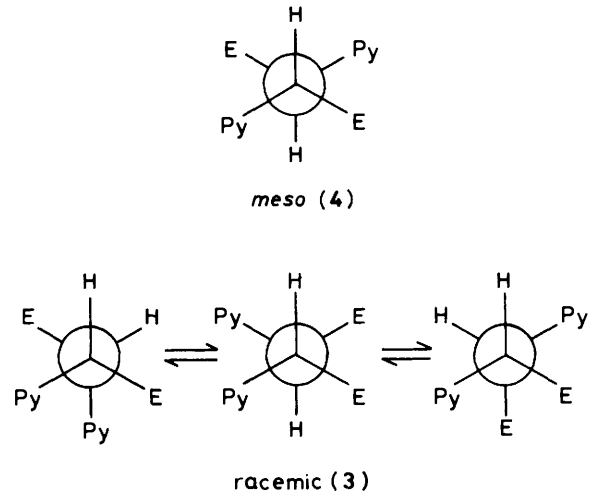


Figure 2.

signal is shielded. By applying these observations on the bisadducts isolated by Reimlinger[5] in the reaction of pyrazole with DMAD, it can be concluded that the isomer of m.p. 167 °C (methanol) is the *meso* diastereoisomer and the compound of m.p. 143 °C (water) is the racemic one. Likewise, the bisadduct isolated by Acheson[2,3] and Diels and Alder[1] in the reaction of 3,5-dimethylpyrazole (**1**) with DMAD, m.p. 188 °C (Table 1), is the *meso* diastereoisomer (**4**).

Finally, one recrystallization from methanol of the reaction mixture carried out in acetonitrile (Table 2, entry 3) afforded pure (**4**); thus, one can assume that in the reaction of DMAD with various *N*H-azoles performed by Acheson[7] the *meso* diastereoisomer was always isolated from the reaction mixture by recrystallization from methanol, while the racemic isomer remained in the mother liquors. Likewise, the fumarate structure tentatively assigned by Acheson and Poulter[2] to the monoaddition product of 3,4,5-trimethylpyrazole to DMAD (Table 1) must be a maleate (*E*-isomer) according to our and Reimlinger's results[4] (i.r. data and experimental results).

It is reasonable to assume that the conformation around the saturated C–C bond having the hydrogen atoms in an antiperiplanar position is also favoured in the racemic diastereoisomer (**3**) (Figure 2). In this conformation, '*gauche*' pyrazole rings are reciprocally shielded and at the same time they shield the contiguous hydrogen atoms, the signals of which appear upfield in this diastereoisomer. The '*gauche*' position of the ester groups in this conformation could also justify the deshielding of its corresponding signals in this diastereoisomer.

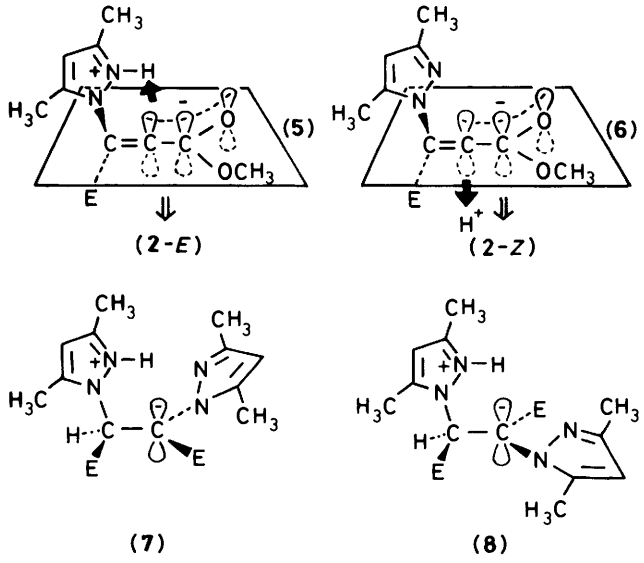
We will discuss the results obtained (Scheme) in the order they take place: first, the initial addition step (**1**) ⟶ (**2**) and then the second one (**2**) ⟶ (**3**) + (**4**).

Addition of 3,5-dimethylpyrazole (**1**) to the triple bond occurs by attack of the iminic nitrogen lone pair giving rise to a betaine (**5**). According to Huisgen,[6] in aprotic solvents an intramolecular proton shift leads to (**2**-*E*), whereas protic solvents, as methanol, protonate C-2 of the anion (**6**) from the less hindered face with concomitant formation of the (**2**-*Z*) olefin. The following results were obtained for the second step

Table 5. N.m.r. chemical shifts (δ values; $CDCl_3$, internal Me_4Si) of (3) and (4)

Compound	3-CH_3	4-H	5-CH_3	C*H*-E	CO_2CH_3
racemic (3)	2.08	5.42	2.08	5.68	3.77
meso (4)	2.20	5.82	2.45	5.92	3.57
		$J_{4,5}$ 0.8,		^3J 10.8 Hz[a]	

[a] From the spectrum recorded in the presence of $Eu(TFC)_3$.



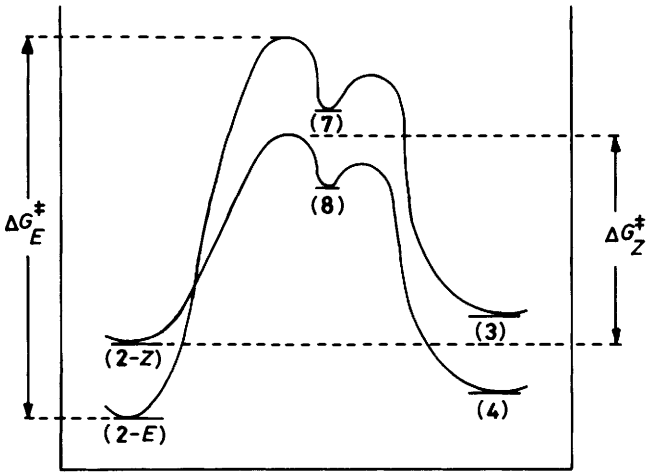


Figure 3. Hypothetical energy profile of the second addition step

(formation of bisadducts). (i) The reaction is stereoselective: (2-*E*) ⟶ (3) and (2-*Z*) ⟶ (4). (ii) The *Z*-olefin is *ca.* 80 times more reactive than the *E*-olefin. (iii) The *Z*-olefin reacts less stereoselectively than the *E*-olefin. (iv) The selectivity is slightly higher in aprotic solvents. Point (iii) is a simple consequence of point (ii) (reactivity–selectivity principle).

Addition of (1) to the double bond of (2-*E*) and (2-*Z*) leads to the carbanions (7) and (8) which are planar due to conjugation with the ester group.

Rotation around the C-1–C-2 bond transforms one intermediate into the other. The observed stereoselectivity shows that the intramolecular proton-shift rate is greater than the rotation rate. Protic solvents compete with the intramolecular process and slightly lower the selectivity.

Two points remain obscure: (ii), what is the origin of the difference in reactivity between both olefins, and (iv), why is the reaction slowed down in methanol? Point (ii) indicates an energy profile of the type represented in Figure 3.

Due to an interaction between both ester groups, the carbanion (7) would be less stable than (8); since equilibration attempts have been unsuccessful for both olefins and bisadducts, the other parts of the profile are only tentative. A more precise discussion needs semiempirical calculations on the nucleophilic addition on the olefins (2-*E*) and (2-*Z*), to determine if the reaction is charge- or orbital-controlled.

Point (iv) seems to correspond to solvation of the lone pair of the pyrazole (1) by the acidic OH of methanol, which lowers its nucleophilic reactivity.

Experimental

M.p.s were determined on a Buchi 510 apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer and the n.m.r. spectra for solutions in $CDCl_3$ using tetramethylsilane as an internal standard on a Varian T-60A spectrometer. Microanalysis were performed at Centro Nacional de Química Orgánica (C.S.I.C., Madrid).

Reaction of 3,5-*Dimethylpyrazole* (1) *with Acetylenic Esters. General Procedure.*—The mixture of reactants in the corresponding solvent, with a concentration of ester between 0.13 and 0.20M, was kept at the temperature and for the time indicated in Tables 1 and 2. When the reaction was finished the solvent was removed *in vacuo* and the whole reaction mixture analysed by ^1H n.m.r.

Reaction with DMAD in methanol for 5 *days at room temperature.* The reaction mixture was recrystallized from methanol until constant m.p. 186—187 °C, yielding *meso-dimethyl* 2,3-*bis*-(3,5-*dimethylpyrazol*-1-*yl*)*succinate* (4), $\nu_{max.}$(KBr) 1 740 and 1 555 cm^{-1} (Found: C, 57.4; H, 6.4; N, 16.8. $C_{16}H_{22}N_4O_4$ requires C, 57.5; H, 6.6; N, 16.8%). Evaporation of the mother liquors and recrystallization of the residue from water until constant m.p. 129—130 °C yielded racemic *dimethyl* 2,3-*bis*-(3,5-*dimethylpyrazol*-1-*yl*)*succinate* (3), $\nu_{max.}$(KBr) 1 745 and 1 560 cm^{-1} (Found: C, 57.5; H, 6.6; N, 17.0. $C_{16}H_{22}N_4O_4$ requires C, 57.5; H, 6.6; N, 16.8%).

Reaction with DMAD in methanol for 20 *hours at room temperature.* The reaction mixture (3.4 g) was chromatographed on silica gel (Merck; 180 g; 70—230 mesh). Elution with benzene–ethyl acetate (9:1) yielded *dimethyl bis*-(3,5-*dimethylpyrazol*-1-*yl*)*maleate* (2-*E*) (1 g), m.p. 57—58 °C (from hexane), $\nu_{max.}$(film) 1 755, 1 710, 1 640, and 1 575 cm^{-1} (Found: C, 55.4; H, 5.8; N, 12.0. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.8%).

After elution of the mixture of bisadducts using the same mixture of solvents as above, elution with benzene–ethyl acetate (85:15) yielded *dimethyl bis*-(3,5-*dimethylpyrazol*-1-*yl*)*fumarate* (2-*Z*) (1.6 g) as a yellow oil, b.p. 116—117 °C at 0.2 mmHg, $\nu_{max.}$(film) 1 735, 1 650, and 1 565 cm^{-1} (Found: C, 55.2; H, 6.3; N, 11.7. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.8%).

Reaction with MP in methanol under reflux. The reaction mixture (650 mg) was chromatographed on silica gel (Merck; 33 g; 70—230 mesh). Elution with benzene–ethyl acetate (95:5) yielded the *E*-monoadduct *methyl* β-(3,5-*dimethylpyrazol*-1-*yl*)*acrylate*, m.p. 55—56 °C (from hexane), $\nu_{max.}$ 1 710, 1 640, and 1 575 cm^{-1} (Found: C, 59.6; H, 7.0; N, 15.3. $C_9H_{12}N_2O_2$ requires C, 60.0; H, 6.7; N, 15.6%).

Elution with benzene–ethyl acetate (9:1) yielded the *Z*-isomer *methyl* β-(3,5-*dimethylpyrazol*-1-*yl*)*acrylate* (416 mg) as an oil,

b.p. 83—84 °C at 0.04 mmHg, $\nu_{max.}$(film) 1 725, 1 660, and 1 570 cm^{-1} (Found: C, 59.7; H, 6.8; N, 15.8. $C_9H_{12}N_2O_2$ requires C, 60.0; H, 6.7; N, 15.6%).

Attempts at Isomerization of the Bisadducts (**3**) *and* (**4**).—The experiments were carried out in n.m.r. tubes; 0.09 mmol of (**3**) or (**4**) were dissolved in 0.5 ml of carbon tetrachloride and the solution was kept at room temperature. The mixtures were checked each 24 h by ^1H n.m.r. After seven days no isomerization was detected. The same results were obtained from an equimolar solution of (**4**) (0.13 mmol) and (**1**) or (**4**) (0.13 mmol) and (**2**-*E*) in carbon tetrachloride (0.5 ml).

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