Reaction of Some 1,2-Diaza-1,3-butadienes with Activated Methine Compounds. A Straightforward Entry to 1,4-Dihydropyridazine, Pyridazine, and 4,5(4*H*,5*H*)-Cyclopropylpyrazole Derivatives

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1-Aminocarbonyl-1,2-diaza-1,3-butadienes with β-tri- or β-dicarbonyl compounds containing at least two keto functions give 1,4-dihydropyridazines, while hydrazone 1,4-adducts are obtained in the case of compounds containing one or no keto function. 1,4-Dihydropyridazines are transformed into pyridazines. The same substrates with 3-phenoxypentane-2,4-dione afford pyridazines. Surprisingly, 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes with methyl 2-acetylacetoacetate produce 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles deriving from 1-alkoxycarbonyl-1,2-dihydropyridazine intermediates by ring contraction. These pyrazole derivatives with acetic acid show ring expansion to 1-alkoxycarbonyl-1,4-dihydropyridazines that can be converted into 1,4-dihydropyridazines with sodium hydroxide. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles or 1-alkoxycarbonyl-1,4-dihydropyridazines with trifluoroacetic acid provide 1-aminopyrroles via 1-alkoxycarbonyl-1,4-dihydropyridazine intermediates in the case of pyrazoles. The X-ray crystal structure of 1-*tert*-butoxycarbonyl-3,5-dimethyl-4-methoxycarbonyl-4,5(4*H*,5*H*)-(methoxycarbonylcyclopropyl)-1*H*-pyrazole was determined.

Introduction

1,2-Diaza-1,3-butadienes have been demonstrated to be powerful tools in organic chemistry[1−3] and, in particular, in the construction of polyfunctionalized pyrrole, pyrazole, thiazole, and imidazole rings.[3−5]

In a previous paper, we preliminarily reported the first synthesis of some 1,4-dihydropyridazines and pyridazines by reaction of 1-aminocarbonyl-1,2-diaza-1,3-butadienes with β-tricarbonyl compounds.[6] In fact, in the course of our activity in this field we have detected, with only one exception,[7] that the reaction between 1,2-diaza-1,3-butadienes and carbonyl compounds containing activated methylene or methine groups always generates pyrrole rather than dihydropyridazine nuclei,[3,8] as erroneously reported by previous authors.[9,10] This occurrence is a consequence of a domino 1,4-addition (Michael-type)-ring annulation reaction by a nucleophilic reagent bearing in the α-position to the attacking carbon atom a ketone, nitrile, or ester function on the azo-ene system of 1,2-diaza-1,3-butadienes,[11] concluding in a [3 + 2] instead of [4 + 2] cyclization process (Scheme 1).[3] Indeed, [4 + 2] cycloadditions of Diels−Alder-type producing tetrahydropyridazine rings have been revealed when 1,2-diaza-

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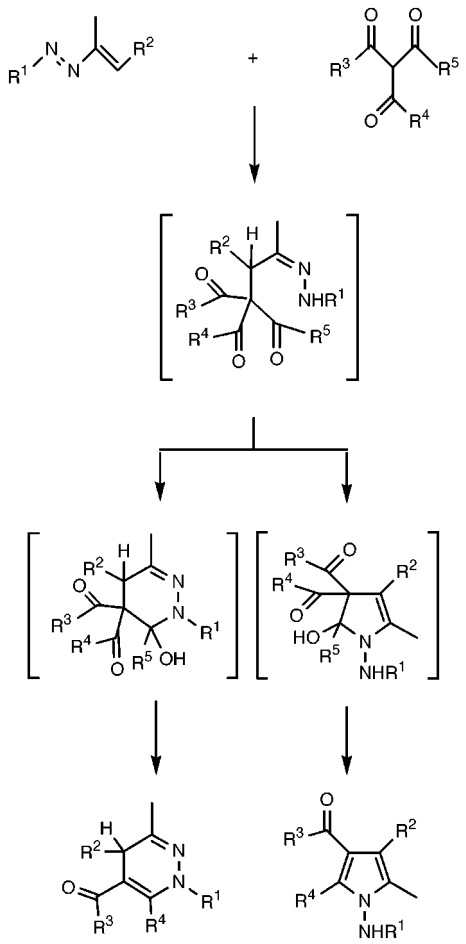
Scheme 1



1,3-butadienes as heterodiene systems were reacted with electron-rich olefins as dienophiles.[1,2,12,13]

The synthesis of pyridazine derivatives has recently received much attention because of their biological activity.[14] In particular, South et al. (Monsanto Corp.) patented pyridazine products exhibiting "bleaching" herbicidal activity prepared from 1,2-diaza-1,3-butadienes.[15]

For these reasons, we decided to investigate more exhaustively the reaction of both 1-aminocarbonyl- and 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes with different β-tri- or β-dicarbonyl compounds containing activated methine groups in order to obtain pyridazine structures. Some interesting diversities in the pathway of these reactions have been observed.

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Results and Discussion

1-Aminocarbonyl-1,2-diaza-1,3-butadienes **1a**−**e** easily react in tetrahydrofuran at room temperature with triacetylmethane **2a** or methyl or ethyl 2-acetylacetoacetate **2b**,**c** in the presence of sodium hydride or potassium carbonate to give in one flask 1-unsubstituted 1,4-dihydropyridazines **5a**−**m** in good to excellent yields (Scheme 2 and Table 1). In most cases, potassium carbonate instead of sodium hydride as previously employed afforded less complicated reaction mixtures and better yields in final products.[6] The mechanism proposed in Scheme 2 is the result of some mechanistic findings presented and discussed in detail below.

Under the same reaction conditions, **1a**,**b** react with diethyl acetylmalonate **6a** or triethyl methanetricarboxylate **6b**, providing in high yields the hydrazones **7a**,**b** by 1,4-addition of β-tricarbonyl derivatives to the azo-ene system (Scheme 3) and supporting the first step of the mechanism proposed in Scheme 2. Since the adducts **7a**,**b** manifest no tendency to produce further reactions, it can be concluded that the presence of one or no keto function is not able to permit the ring closing owing to the elimination of an acetic acid molecule.

The reaction under usual conditions between **1a**,**d**,**e** and ethyl 2-(2-furoyl)acetoacetate **2d** or ethyl 2-(2-thenoyl)-acetoacetate **2e** produces a mixture of 1-unsubstituted 6-methyl- and 1-unsubstituted 6-(2-furoyl)-1,4-dihydropyridazines **5c**,**j**,**m** or 1-unsubstituted 6-(2-thenoyl)-1,4-dihydropyridazines **5n**−**r** in a similar ratio. This occurrence is likely due to the nearly equivalent possibility of ring closing on the two different keto groups of the hypothesized intermediates **3** (Scheme 4 and Table 1). The pathway A leads to the same compounds **5c**,**j**,**m** depicted above (Scheme 2), while the pathway B leads to new compounds **5n**−**r** with a furoyl or thenoyl ring as substituent.

The reaction of **1a**,**b**,**d**,**e** with 3-phenylpentane-2,4-dione **2f** or 3-(2-chloro-6-fluorobenzyl)pentane-2,4-dione **2g** under the same conditions gives rise in one pot to 1-unsubstituted 1,4-dihydropyridazines **5s**−**v** in good yields (Scheme 5 and Table 1). This behavior proves that this procedure can be successfully applicable also to compounds possessing an activated β-dicarbonyl methine group.

The conversion of **5a**−**v** into the corresponding pyridazines **9a**−**v** in nearly quantitative yields was achieved by bromination of the carbon atom in position 4 with tribromide on Amberlyst A-26 in methylene chloride at room temperature (Scheme 6 and Table 2). The use of this solid-phase brominating reagent implicated remarkable improvements with respect to phenyltrimethylammonium tribromide previously utilized by virtue of the minor presence of reaction byproducts,[6] both in terms of regioselectivity and yields.[16] Furthermore, this polymer-supported brominating agent is more convenient than phenyltrimethylammonium tribromide also due to its easy regeneration and the simpler manipulation of the reaction mixture (only filtration).[17] The expected brominated intermediates **8** were not isolated because of the ready dehydrobromination process.[6]

Pyridazines **9a**,**d**,**f**,**h**,**k** have been directly obtained as exclusive products when **1a**−**e** were reacted in tetrahy-

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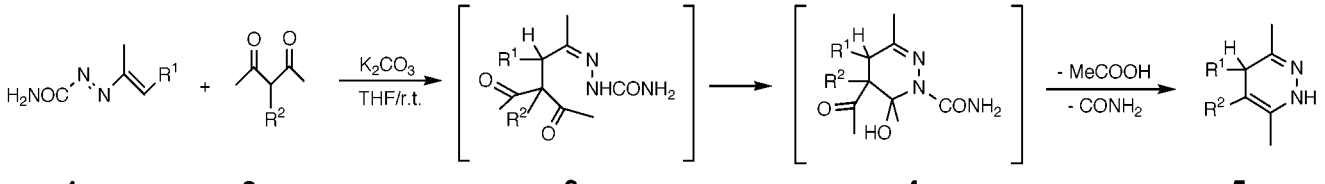
Scheme 2



1a-e **2a-c** **3** **4** **5a-m**

1a: R^1 = COOMe
1b: R^1 = COOEt
1c: R^1 = COO*t*-Bu
1d: R^1 = $COO(CH_2)_2OMe$
1e: R^1 = $COOCH_2Ph$

2a: R^2 = COMe
2b: R^2 = COOMe
2c: R^2 = COOEt

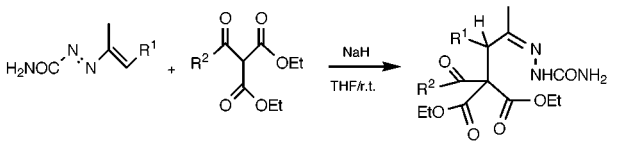
Table 1. Yields of 1-Unsubstituted-1,4-Dihydropyridazines 5a−v

Entry	R^1	R^2	Yield[a] (%)
5a	COOMe	COMe	84
5b	COOMe	COOMe	90
5c	COOMe	COOEt	58
5d	COOEt	COMe	87
5e	COOEt	COOMe	88
5f	COO*t*-Bu	COMe	69
5g	COO*t*-Bu	COOMe	83
5h	$COO(CH_2)_2OMe$	COMe	57
5i	$COO(CH_2)_2OMe$	COOMe	54
5j	$COO(CH_2)_2OMe$	COOEt	57
5k	$COOCH_2Ph$	COMe	75
5l	$COOCH_2Ph$	COOMe	74
5m	$COOCH_2Ph$	COOEt	87
5n	COOMe		43
5o	COOMe		33
5p	$COO(CH_2)_2OMe$		40
5q	$COO(CH_2)_2OMe$		34
5r	$COOCH_2Ph$		37
5s	COOMe	Ph	42
5t	COOEt		43
5u	$COO(CH_2)_2OMe$		57
5v	$COOCH_2Ph$		61

[a]Yield of pure isolated products.

drofuran at room temperature with 3-phenoxypentane-2,4-dione **2h** in the presence of potassium carbonate. In this case, the intermediates **3** and **4**, as well as the product **5**, were not detected probably because of a rapid aromatization process due to the loss of phenol and carbammic acid residues (Scheme 7).

Scheme 3



1a,b **6a,b** **7a,b**

1a: R^1 = COOMe
1b: R^1 = COOEt

6a: R^2 = Me
6b: R^2 = OEt

7a: R^1 = COOMe, R^2 = Me (84 %)
7b: R^1 = COOEt, R^2 =OEt (91 %)

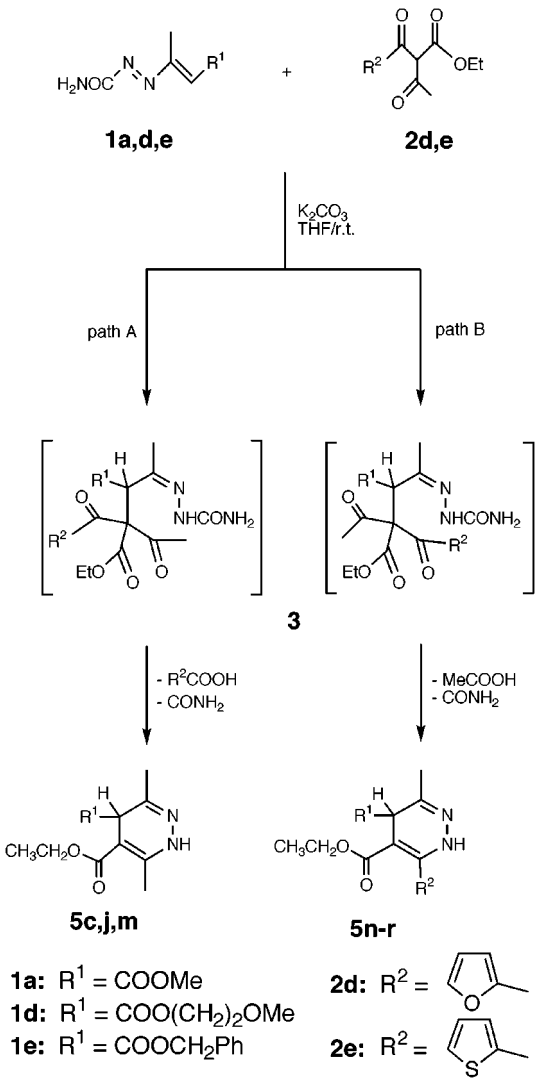
Surprisingly, the reaction between 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes **1f−h** and methyl 2-acetylacetoacetate **2b** in tetrahydrofuran at room temperature in the presence of potassium carbonate offered 1-alkoxycarbonyl-1,4-dihydropyridazines **14a−c** and then 1-unsubstituted 1,4-dihydropyridazines **5b**,**e** by means of a more complicated mechanism compared with that of analogous **1a−e**. A detailed study of some reaction products and intermediates allowed us to obtain interesting mechanistic information.

Indeed, when the reaction was carried out under the usual conditions (Scheme 2) the isolated products were different from the expected **5b**,**e** as well as from **14a−c**. In fact, the spectroscopic data revealed that the substituent group linked to the nitrogen heteroatom of this product is still present, while in **5b**,**e** the same group is absent. Moreover, ^1H and ^{13}C NMR spectra exhibit similar resonances as for **14a−c** but with some significant differences: (i) a large upfield shift of methine proton (from ~4.5 to ~2.8 ppm) in ^1H NMR spectra; (ii) the presence of three C-sp^3 signals (~26.3, ~50.1, and ~59.0 ppm) instead of only one C-sp^3 resonance (~44.7 ppm) of compound **5b**,**e**; (iii) the coupling constant value for the carbon that resonates at ~26.3 ppm is $J_{CH} = 165$ Hz, typical for a CH in a cyclopropane ring.

Therefore, all spectroscopical evidence should be fitted with molecules having the structure of 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles **13a−c**. X-ray diffraction investigations were undertaken for **13c**, as a model able to prove unambiguously the structure assigned to these compounds. The crystal parameters of such a molecular model inequivocally confirmed our hypothesis (Figure 1).

In particular, the TLC analysis of the reaction mixtures reveals two other spots with higher polarity than **13a−**

Scheme 4



c. Attempts to isolate the more polar one were unsuccessfull because of its quick transformation in the middle one followed by its conversion in **13a**−**c**. However, it was possible to isolate a small amount of pure middle products that demonstrated to be the 1-alkoxycarbonyl-1,2,5,6-tetrahydropyridazine derivatives **11a**−**c** by ^{1}H NMR and MS spectroscopy, mainly due to the OH and NH signals at ∼6.77 and ∼12.84 ppm, respectively, as well as to the presence of two different methyl group signals at ∼1.92 and ∼2.45 ppm, respectively, attributable to two acetyl groups of the starting methyl 2-acetylacetoacetate. In tetrahydrofuran, this compound spontaneously generated exclusively **13a**−**c**. Thus, we suppose that the greatest polar spot corresponds to the transient hydrazone 1,4-adduct **10**.

On the basis of this evidence, it seems reasonable to conclude that the reaction takes place by means of a preliminary 1,4-addition of **2b** to the substrates **1f**−**h** as consequence of the nucleophilic attack by the activated methine group on the heterodiene system producing the hydrazone intermediate **10**. The subsequent intramolecular nucleophilic attack by the terminal hydrazone nitrogen atom to the carbonyl function determines the closing of **11a**−**c**. The elimination of an acetic acid molecule from this last intermediate furnishes **12**, which affords **13a**−**c** owing to ring contraction of the six- to five-membered heterocycle (Scheme 8).

Further proof of the interconversion between these heterocyclic structures was furnished upon reaction of **13a**−**c** with acetic acid at room temperature, determining ring expansion to **14a**−**c** that in turn afforded **5b**,**e** by cleavage with sodium hydroxide in methanol at room temperature (Scheme 9).

In our opinion, the preliminary hydrazone intermediates **3** and **10** in the reactions both of **1a**−**e** and **1f**−**h** with activated methine compounds previously detected in similar circumstances[3] and indirectly supported by the 1,4-adducts **7a**,**b** can be considered common for all these reactions. However, the absence of any detectable intermediate, as well as the concomitant loss of the $CONH_2$ group, in the case of **1a**−**e** hinder us to extend in toto or in part the remaining detailed mechanism established for the reactions of **1f**−**h** on the basis of isolable intermediates.

When **13a**−**c** were reacted with trifluoroacetic acid at room temperature (**13c**) or under reflux (**13a**,**b**), the corresponding 1-aminopyrroles **15a**−**c** were recovered. The same products were obtained when **14a**−**c** were submitted to the same reaction (Scheme 10). In both cases, **5b**,**e** were revealed as side products of these reactions.

Therefore, taking into account the reaction pathway depicted in Scheme 9, the formation of **15a**−**c** from **13a**−**c** involves **14a**−**c** as intermediates. In some cases, in fact, these intermediates can be isolated by column chromatography from the reaction mixtures when the reactions are interrupted before the complete conversion of **13a**−**c** into **15a**−**c**.

Conclusion

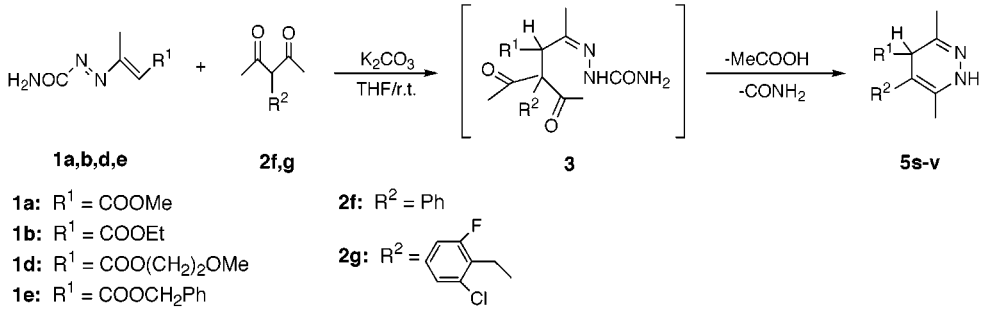
The reaction of 1-aminocarbonyl-1,2-diaza-1,3-butadienes with activated methine compounds represents a straightforward entry to 1,4-dihydropyridazine and pyridazine derivatives. Surprisingly, the analogous reaction between 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes and methyl 2-acetylacetoacetate produces 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles. A detailed investigation of the reaction pathway demonstrated that these compounds derive from 1-alkoxycarbonyl-1,2-dihydropyridazine intermediates by ring contraction. Ring expansion of 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles leads to 1-alkoxycarbonyl-1,4-dihydropyridazines that can be converted into 1-unsubstituted 1,4-dihydropyridazines. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles and 1-alkoxycarbonyl-1,4-dihydropyridazines separately give 1-aminopyrroles via 1-alkoxycarbonyl-1,4-dihydropyridazine intermediates in the case of 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles.

In conclusion, this paper reports not only useful access to new heterocyclic systems but also deals with some interesting interconversions of five-membered rings of pyrazole type into six-membered rings of the 1,4-dihydropyridazine type and then the last one into some five-membered rings of the pyrrole type by ring opening−closing mechanisms.

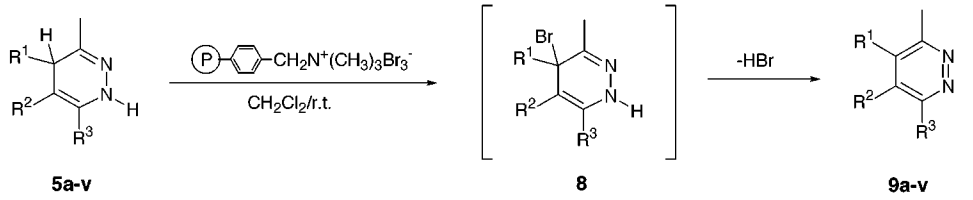
Experimental Section

General Methods. 1-Aminocarbonyl-1,2-diaza-1,3-butadienes **1a**−**e** and 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes **1f**−**h** were synthesized according to previously reported

Scheme 5



Scheme 6



procedures.[18,19] Starting materials of the above-mentioned reagents, as well as triacetylmethane (**2a**), methyl (**2b**) and ethyl 2-acetylacetoacetates (**2c**), diethyl acetylmalonate (**6a**), triethyl methanetricarboxylate (**6b**), ethyl 2-(2-furoyl)acetoacetate (**2d**), ethyl 2-(2-thenoyl)acetoacetate (**2e**), 3-phenylpentane-2,4-dione (**2f**), 3-(2-chloro-6-fluorobenzyl)pentane-2,4-dione (**2g**), 3-phenoxypentane-2,4-dione (**2h**), tribromide on Amberlyst A-26, sodium hydride, sodium hydroxide, potassium carbonate, trifluoroacetic acid, acetic acid, and solvents are commercially available materials (Carlo Erba, Aldrich, Acros, Fluka, Lancaster, Avocado, and Maybridge) and were used without further purification. Melting points were determined in open capillary tubes and are uncorrected. The products often decompose at the melting point. IR−FT spectra were performed in Nujol mull. MS spectra were made at an ionizing voltage of 70 eV. ^{1}H NMR spectra were recorded at 200 MHz, while ^{13}C NMR were recorded spectra at 50.32 MHz. Chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants (J) in Hz. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Precoated silica gel plates 0.25 mm were employed for analytical thin-layer chromatography and silica gel 35−70 μm for column chromatography.

Preparation of 1-Unsubstituted 1,4-Dihydropyridazines 5a−v. To a stirred solution of triacetylmethane (**2a**), methyl 2-acetylacetoacetate (**2b**), ethyl 2-acetylacetoacetate (**2c**), ethyl 2-(2-furoyl)acetoacetate (**2d**), ethyl 2-(2-thenoyl)acetoacetate (**2e**), or 3-(2-chloro-6-fluorobenzyl)pentane (**2g**) (1 mmol) in tetrahydrofuran (10 mL) was added potassium carbonate (4 mmol). In the case of 3-phenylpentane-2,4-dione (**2f**) (1 mmol), a catalytic amount of sodium hydride (0.3 mmol) instead of potassium carbonate was added**.** The reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then the 1-aminocarbonyl-1,2-diaza-1,3-butadiene **1a**−**e** (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (∼10 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording 1,4-dihydropyridazines **5a**−**v** that were crystallized from ethyl acetate−petroleum ether (40−60 °C).

5a: mp 63−65 °C; IR (Nujol) ν_{max} 3281, 1705, 1688, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H, Me), 2.14 (s, 3H, Me), 2.31 (s, 3H, Me), 3.72 (s, 3H, CO_2*Me*), 4.31 (s, 1H, CH), 7.55 (br s, 1H, NH, D_2O-exch); ^{13}C NMR ($CDCl_3$) δ 17.9 (Me), 22.3 (Me), 27.6 (Me), 51.2 (C4), 51.5 (CO_2*Me*), 89.6 (C5), 145.7 and 147.2 (C3 and C6), 167.2 (COO), 204.9 (CO); MS *m*/*z* 210 (2) [M$^+$], 179 (5), 167 (100). Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.06; H. 6.65, N. 13.36.

5b: mp 94−96 °C. IR (Nujol) ν_{max} 3283, 1724, 1688, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H, Me), 2.32 (s, 3H, Me), 3.69 (s, 3H, CO_2*Me*), 3.71 (s, 3H, CO_2*Me*), 4.35 (s, 1 H, CH), 7.77 (br s, 1H, NH, D_2O-exch); ^{13}C NMR ($CDCl_3$) δ 17.6 (Me), 22.2 (Me), 43.2 (C4), 51.0 (CO_2*Me*), 52.3 (CO_2*Me*), 89.0 (C5), 143.7 and 147.2 (C3 and C6), 167.2 (COO), 170.5 (COO); MS *m*/*z* 226 (5) [M$^+$], 195 (4), 167 (100). Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09, H. 6.24, N. 12.38. Found: C, 53.17, H. 6.32, N. 12.46.

Preparation of Hydrazones 7a,b. To a stirred solution of diethyl acetylmalonate (**6a**) or triethyl methanetricarboxylate (**6b**) (1 mmol) in tetrahydrofuran (10 mL) was added potassium carbonate (4 mmol). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then the 1-aminocarbonyl-1,2-diaza-1,3-butadiene **1a**,**b** (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (∼10 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording hydrazones **7a**,**b** that were crystallized from ethyl acetate−petroleum ether (40−60 °C).

7a: mp 103−105 °C; IR (Nujol) ν_{max} 3499, 3387, 1757, 1747, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 9H J = 7.1 Hz, 3 × CO_2CH_2*Me*), 2.03 (s, 3H, Me), 3.74 (s, 3H, CO_2*Me*), 4.19−4.33 (m, 7H, 3 × CO_2*CH*$_2$Me and CH), 5.82 (br s, 2H, NH_2, D_2O-exch), 9.00 (br s, 1H, NH, D_2O-exch); ^{13}C NMR ($CDCl_3$) δ 13.7 (3 × Me), 17.0 (Me), 52.4 (CO_2*Me*), 55.4 (CH), 62.5 (3 × CO_2*CH*$_2$Me), 67.0 (*C*(CO)$_3$), 143.9 ($CONH_2$), 158.2 (CN), 165.6 (3 × COO), 169.2 (COO); MS *m*/*z* 403 (2) [M$^+$], 326 (9), 255 (11), 183 (100). Anal. Calcd for $C_{16}H_{25}N_3O_9$: C, 47.64; H, 6.25; N, 10.42. Found: C, 47.81; H, 6.35; N, 10.37.

Preparation of Pyridazines 9a−v from Reaction of 1,4-Dihydropyridazines 5a−v with Tribromide on Amberlist A-26. To a stirred solution of 1,4-dihydropyridazine **5a**−**v** (1 mmol) in dichloromethane (10 mL) was added tribromide on Amberlist A-26 (1 mmol). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 2 h and then was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording pyridazines **9a**−**v** that were crystallized from ethyl acetate−petroleum ether (40−60 °C).

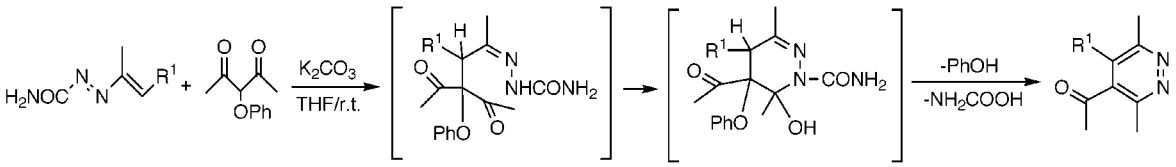
(18) Sommer, S. *Tetrahedron Lett.* **1977**, *18*, 117.
(19) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 873. Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671.

Table 2. Yields of Pyridazines 9a–v

Entry **5** and **9**	R^1	R^2	R^3	Yield (%)[a]
a	COOMe	COMe	Me	89
b	COOMe	COOMe	Me	93
c	COOMe	COOEt	Me	93
d	COOEt	COMe	Me	86
e	COOEt	COOMe	Me	89
f	COO*t*-Bu	COMe	Me	91
g	COO*t*-Bu	COOMe	Me	91
h	$COO(CH_2)_2OMe$	COMe	Me	84
i	$COO(CH_2)_2OMe$	COOMe	Me	92
j	$COO(CH_2)_2OMe$	COOEt	Me	93
k	$COOCH_2Ph$	COMe	Me	83
l	$COOCH_2Ph$	COOMe	Me	94
m	$COOCH_2Ph$	COOEt	Me	93
n	COOMe	COOEt		89
o	COOMe	COOEt		94
p	$COO(CH_2)_2OMe$	COOEt		85
q	$COO(CH_2)_2OMe$	COOEt		87
r	$COOCH_2Ph$	COOEt		96
s	COOMe	Ph	Me	87
t	COOEt		Me	84
u	$COO(CH_2)_2OMe$		Me	86
v	$COOCH_2Ph$		Me	92

[a]Yield of pure isolated products.

Scheme 7



1a-e **2h** **3** **4** **9a,d,f,h,k**

1a, 9a: R^1 = COOMe
1b, 9d: R^1 = COOEt
1c, 9f: R^1 = COO*t*-Bu
1d, 9h: R^1 = $COO(CH_2)_2OMe$
1e, 9k: R^1 = $COOCH_2Ph$

9a (78 %)
9d (72 %)
9f (68 %)
9h (73 %)
9k (88 %)

9a: mp 61–63 °C; IR (Nujol) ν_{max} 1723, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, Me), 2.67 (s, 3H, Me), 2.84 (s, 3H, Me), 3,92 (s, 3H, CO_2*Me*).^{13}C NMR ($CDCl_3$) δ 19.7 (Me), 21.5 (Me), 30.8 (Me), 53.1 (CO_2*Me*), 124.7 and 138.3 (C4 and C5), 152.9 and 155.7 (C3 and C6), 165.5 (COO), 201.1 (CO); MS *m*/*z* 208 (100) [M^+]. Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.63; H, 5.85; N, 13.36.

9b: mp 66–68 °C; IR (Nujol) ν_{max} 1726, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (s, 6H, 2 × Me), 3.96 (s, 6H, 2 × CO_2*Me*); ^{13}C NMR ($CDCl_3$) δ 20.7 (2 × Me), 53.1 (2 × CO_2*Me*), 128.0 (C4 and C5), 155.1 (C3 and C6), 165.6 (2 × COO); MS *m*/*z* 224 (100) [M^+]. Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.61; H, 5.46; N, 12.47.

Preparation of Pyridazines 9a,d,f,h,k from Reaction of 1-Aminocarbonyl-1,2-diaza-1,3-butadienes 1a–e with 3-Phenoxypentane-2,4-dione (2h). To a stirred solution of 3-phenoxypentane-2,4-dione (**2h**) (1 mmol) in tetrahydrofuran (10 mL) was added potassium carbonate (4 mmol). The

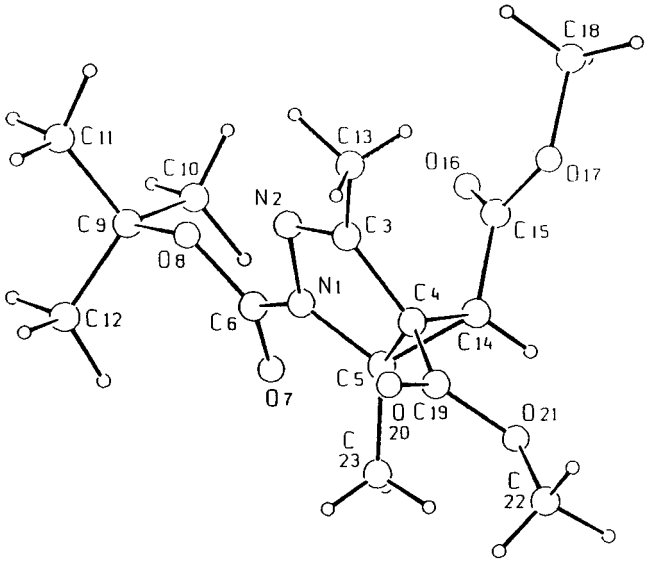


Figure 1. X-ray molecular structure of 1-*tert*-butoxycarbonyl-3,5-dimethyl-4-methoxycarbonyl-4,5(4*H*,5*H*)-(methoxycarbonylcyclopropyl)-1*H*-pyrazole (**13c**) with the atom numbering system used in the crystallographic analysis.

reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then 1-aminocarbonyl-1,2-diaza-1,3-butadiene **1a**−**e** (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (∼20 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording pyridazines **9a** (78%), **9d** (72%), **9f** (68%), **9h** (73%), and **9k** (88%) that were crystallized from ethyl acetate−petroleum ether (40−60 °C).

Preparation of 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles 13a−c. To a stirred solution of methyl 2-acetylacetoacetate (**2b**) (1 mmol) in tetrahydrofuran (5 mL) was added potassium carbonate (4 mmol). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 min, and then 1-alkoxycarbonyl-1,2-diaza-1,3-butadiene **1f**−**h** (1 mmol) in tetrahydrofuran (5 mL) was added dropwise until its red color disappeared (∼10 min). Stirring was continued for 2 h, and then the reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording 1-alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles **13a**−**c** that were crystallized from ethyl acetate−petroleum ether (40−60 °C). To isolate the intermediates **11a**−**c**, the reaction mixture was filtered, concentrated under reduced pressure, and rapidly chromatographed as soon as the red color of 1-alkoxycarbonyl-1,2-diaza-1,3-butadiene **1f**−**h** disappeared.

11a: ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H, Me), 2.08 (s, 3H, Me), 2.45 (s, 3H, Me), 3.71 (s, 6H, 2 × CO_2*Me*), 3.76 (s, 3H, CO_2*Me*), 6.79 (br s, 1H, OH, D_2O, exch), 12.84 (br s, 1H, NH, D_2O, exch); MS *m*/*z* 344 (2) [M^+], 302 (5), 284 (18), 252 (50), 227 (56), 213 (48), 181 (100).

13a: mp 57−59 °C; IR (Nujol) ν_{max} 1745, 1724, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H, Me), 2.25 (s, 3H, Me), 2.82 (s, 1H, CH), 3.64 (s, 3H, CO_2*Me*), 3.84 (s, 3H, CO_2*Me*), 3.87 (s, 3H, CO_2*Me*); ^{13}C NMR ($CDCl_3$) δ 15.0 (Me), 15.4 (Me), 26.5 (CH), 50.1 (C4), 51.6 (CO_2*Me*), 52.5 (CO_2*Me*), 52.9 (CO_2*Me*), 59.2 (C5), 149.4 and 152.5 (C3 and NCO_2), 164.5 (COO), 165.0 (COO); MS *m*/*z* 284 (35) [M^+], 252 (100). Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.67; H, 5.65; N, 9.89.

Preparation of 1-Alkoxycarbonyl-1,4-Dihydropyridazines 14a−c. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazole **13a**−**c** (1 mmol) was dissolved in acetic acid (5 mL), and the reaction mixture was allowed to stand at room temperature under magnetic stirring for 10 min. Acetic acid was evaporated under reduced pressure, and the residue was dissolved with ethyl acetate (20 mL) and washed with aqueous (20%) sodium carbonate (3 × 20 mL) and then with water (3 × 20 mL). The crude was chromatographed on a silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording 1-alkoxycarbonyl-1,4-dihydropyridazines **14a**−**c** that were crystallized from ethyl acetate−petroleum ether (40−60 °C).

14a: mp 68−69 °C; IR (Nujol) ν_{max} 1739, 1716, 1704, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, Me), 2.65 (s, 3H, Me), 3.68 (s, 3H, CO_2*Me*), 3.79 (s, 3H, CO_2*Me*), 3.92 (s, 3H, CO_2*Me*), 4.55 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 17.7 (Me), 21.8 (Me), 44.3 (C4), 51.5 (CO_2*Me*), 52.4 (CO_2*Me*), 53.6 (CO_2*Me*), 104.4 (C5), 146.8 (NCO_2), 151.3 and 151.9 (C3 and C6), 165.5 (COO), 167.4 (COO); MS *m*/*z* 284 (5) [M^+], 253 (8), 225 (100). Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.73; H, 5.63; N, 9.86.

Preparation of 1-Unsubstituted 1,4-Dihydropyridazines 5b,e from 1-Alkoxycarbonyl-1,4-dihydropyridazines 14a−c. 1-Alkoxycarbonyl-1,4-dihydropyridazine **14a**−**c** (1 mmol) was dissolved in a 1 M methanolic solution of sodium hydroxide (5 mL) and allowed to stand at room temperature under magnetic stirring for 15 min. Methanol was evaporated under reduced pressure, the residue was dissolved with ethyl acetate (40 mL) and then washed with water (3 × 25 mL) affording 1-unsubstituted 1,4-dihydropyridazines **5b**,**e** in nearly quantitative yields that were crystallized from ethyl acetate−petroleum ether (40−60 °C).

Preparation of 1-Aminopyrroles 15a−c from 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazoles 13a−c. 1-Alkoxycarbonyl-4,5(4*H*,5*H*)-(alkoxycarbonylcyclopropyl)pyrazole **13a**−**c** (1 mmol) was dissolved in trifluoroacetic acid (5 mL), and the reaction mixture was heated under reflux for 2 h (**13a**,**b**), or allowed to stand at room temperature under magnetic stirring for 15 min (**13c**). Trifluoroacetic acid was evaporated under reduced pressure, and the residue was dissolved with ethyl acetate (20 mL) washed with aqueous (20%) sodium carbonate (3 × 20 mL) and then with water (3 × 20 mL). The crude was chromatographed on silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording 1-aminopyrroles **15a**−**c** in good yields that were crystallized from ethyl acetate−pentane.

Preparation of 1-Aminopyrroles 15a−c from 1-Alkoxycarbonyl-1,4-dihydropyridazines 14a−c. 1-Alkoxycarbonyl-1,4-dihydropyridazine **14a**−**c** (1 mmol) was dissolved in trifluoroacetic acid (5 mL), and the reaction mixture was heated under reflux for 2 h (**14a**,**b**), or allowed to stand at room temperature under magnetic stirring for 15 min (**14c**). Trifluoroacetic acid was evaporated under reduced pressure, and the residue was dissolved with ethyl acetate (20 mL) and washed with aqueous (20%) sodium carbonate (3 × 20 mL) and then with water (3 × 20 mL). The crude was chromatographed on silica gel column (elution with cyclohexane−ethyl acetate mixtures), affording 1-aminopyrroles **15a**−**c** that were crystallized from ethyl acetate−pentane.

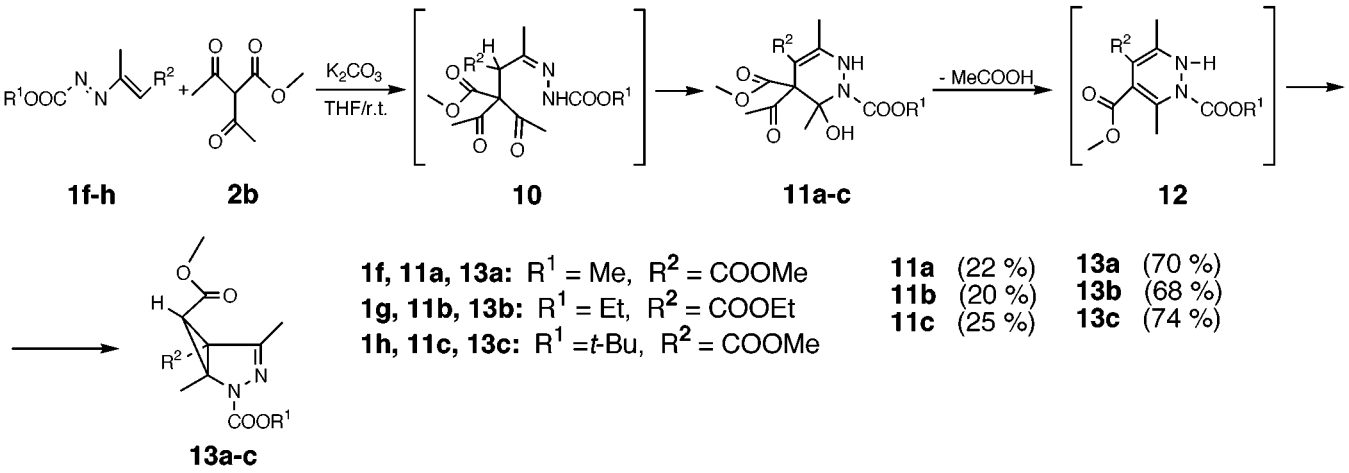
15a.[10f,20]

15b: mp 70−72 °C; IR (Nujol) ν_{max} 3238, 1761, 1713, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.1 Hz, 2 × CO_2-CH_2*Me*), 2.12 (s, 6H, 2 × Me), 3.76 (s, 3H, CO_2*Me*), 4.24 (q, 4H, J = 7.1 Hz, 2 × CO_2CH_2Me), 8.39 (br s, 1H, NH, D_2O, exch); ^{13}C NMR ($CDCl_3$) 9.7 (2 × Me), 14.2 (Me), 14.4 (Me), 51.5 (CO_2*Me*), 60.4 (CO_2CH_2Me), 62.6 (CO_2CH_2Me), 109.8 and 110.1 (C3 and C6), 134.6 (C2 and C5), 154.8 (NHCO), 165.5 (COO), 166.0 (COO); MS *m*/*z* 312 (35) [M^+], 280 (68), 266 (100). Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.78; H, 6.50; N, 8.91.

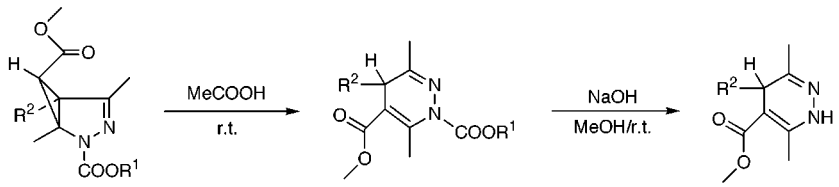
Crystal data: $C_{15}H_{22}N_2O_6$, M = 326.35, monoclinic, space group $P2_1/n$, a = 13.454(8) Å, b = 9.506(2) Å, c = 13.570(6) Å, β = 100.09(5)°, U = 1709(2) Å^3, Z = 4, D_c = 1.27 Mg m^{-3}, F(000)

(20) Attanasi, O. A.; Filippone, P.; Mei, A.; Serra-Zanetti, F. *Synth. Commun.* **1986**, *16*, 343.

Scheme 8

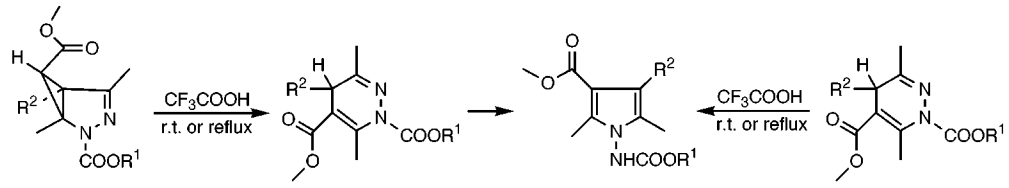


Scheme 9



13a, 14a: R^1 = Me, R^2 = COOMe
13b, 14b: R^1 = Et, R^2 = COOEt
13c, 14c: R^1 = *t*-Bu, R^2 = COOMe

Scheme 10



13a, 14a, 15a: R^1 = Me, R^2 = COOMe
13b, 14b, 15b: R^1 = Et, R^2 = COOEt
13c, 14c, 15c: R^1 = *t*-Bu, R^2 = COOMe

14a (75 %) **14b** (80 %) **14c** (82 %)
15a (88 %) **15b** (87 %) **15c** (92 %)

= 696, λ = 0.710 69 Å, T = 293 K, (Mo Kα) μ = 0.098 mm^{-1}, crystal dimensions 0.50 × 0.70 × 0.30 mm. A total of 3148 reflections were collected (3013 unique, R_{int} = 0.0099).

Data Collection and Processing. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Mo Kα radiation, $\omega/2\theta$ scan mode, range 2.63° < θ < 25.02°.The unit cell parameters were determinated by least-squares refinement on diffractometer angles for 25 automatically centered reflections 7.9° < θ < 12.6°.

Structure Analysis and Refinement. The structure was solved by direct methods and refined by full-matrix least-squares on F^2, using the SHELX program packages.[21,22] In the final refinement cycles 2338 reflections having $I > 2\sigma(I)$ were used, with 209 parameters varied. In refinements were used weights in accord with the scheme $w = 1/[\sigma^2(F_o^2) + (0.0782P)^2 + 0.5678P]$ where $P = (F_o^2 + 2F_c^2)/3$. The hydrogen atoms were located by geometrical calculation and refined using a "riding" model. The final agreement indices were $R_1 = 0.0439$ and $wR_2 = 0.1252$. Goodness of fit on $F^2 = 1.047$. Largest difference peak and hole was 0.312 and −0.236 e Å^{-3}. Full crystallographic results for this X-ray determination have been deposited with the Cambridge Crystallographic Data Centre.

Acknowledgment. This investigation was supported by the financial assistance from the Università degli Studi di Urbino, Consiglio Nazionale delle Ricerche (CNR-Roma) and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST-Roma).

Supporting Information Available: Experimental procedures (13 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.

JO9816515

(21) Sheldrick, G. M. SHELXS-86. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
(22) Sheldrick, G. M. SHELXL-93. *Program for Crystal Structure Refinement*; University of Göttingen, Germany, 1993.