

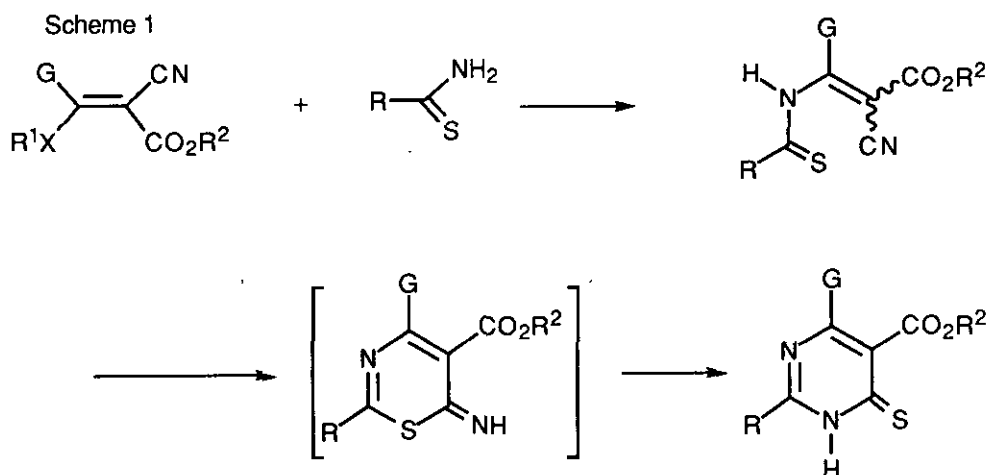
REGIOSELECTIVE SYNTHESIS OF PYRIMIDINES FROM KETENE
DITHIOACETALS OR ALKOXYMETHYLENE COMPOUNDS

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Abstract- Regioselective cyclizations of the condensation products
obtained by the reaction of nitrogen nucleophiles with ketene
dithioacetals or alkoxyethylene compounds are reported.
Stereochemical factors or geometry of the carbon-carbon double
bond determine the regioselectivity of heterocyclization processes.

The synthesis of substituted pyrimidines from thioamides and methoxymethylene compounds or ketene dithioacetals has been previously reported.¹⁻⁴ The reaction proceeds through the condensation product which cyclizes regioselectively by attack of the sulfur to the cyano group, none of the product resulting from cyclization at the alkoxy-carbonyl group being isolated. Regioselective cyclization can be attributed to stereoelectronic control or alternatively to the configuration of the carbon-carbon double bond of the condensation product.

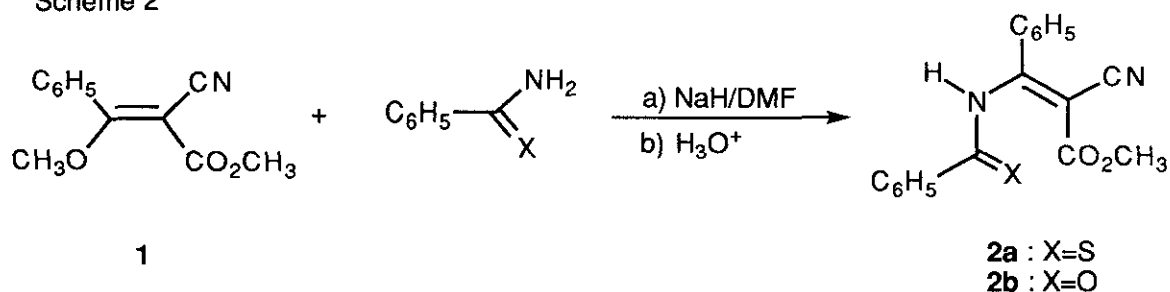


With the purpose of discerning the factors which determine the regioselectivity of these heterocyclization processes, in this paper we describe the reactivity of benzamide, thiobenzamide, benzimidine and thiourea with alkoxyethylene compounds or ketene dithioacetals.

SYNTHESIS OF PYRIMIDINES FROM AMIDES OR THIOAMIDES

Firstly we carried out the reaction of benzamide or thiobenzamide with the methyl 2-cyano-3-phenylpropenoate (**1**), which afforded methyl (Z)-2-cyano-3-benzamido(or thiobenzamido)-3-phenylpropenoates (**2 a,b**).

Scheme 2



The configuration of the C3-C4 double bond, of adducts (**2a**) and (**2b**) was established from X-Ray diffraction and ¹H nmr respectively.

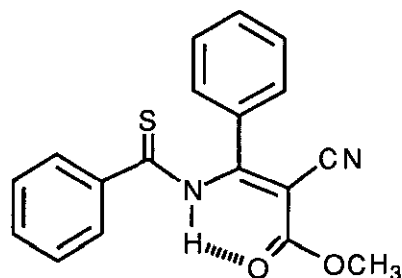


Figure 1. Model illustration of **2a**

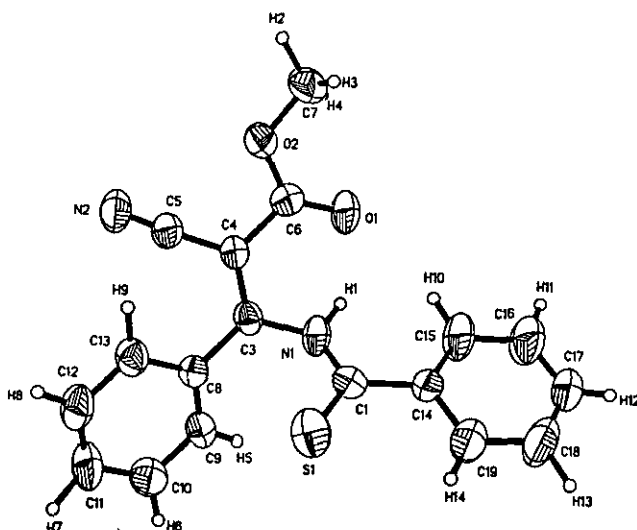


Figure 2. Ortep view of **2a**

Table 1 shows selected geometric parameters for **2a**. Bond angle values show that N1 is sp² hybridized although the NH...O=C hydrogen bond (O1-N1 and O1-H1 distances are 1.893 and 2.678 Å, respectively) contracts the H(1)-N(1)-C(3) bond angle whereas the C(3)-N(1)-C(1) angle

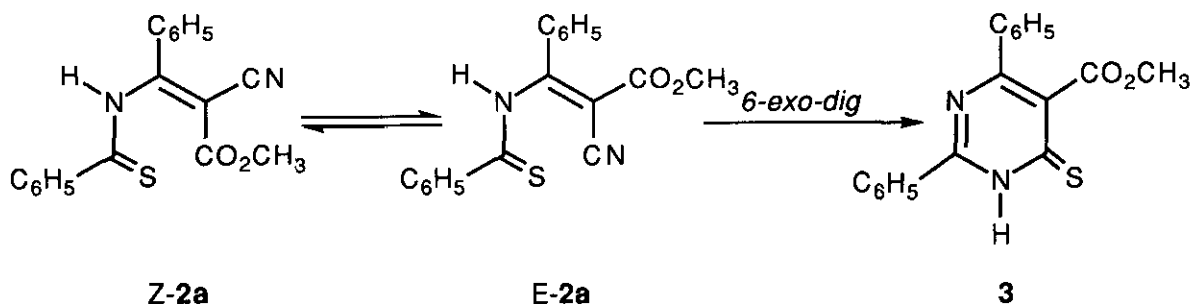
is correspondingly expanded. This hydrogen bond causes the methoxycarbonyl group to deviate from the coplanarity with the C3-C4 double bond. Torsion angle values show that the phenyl group on C3 is conjugated with the C3-C4 double bond. In the same fashion the nonbonding electrons of N1 are conjugated with the thiobenzoyl group, whereas the conjugation with the C3-C4 double bond and phenyl group on C3 is diminished. One of the factors which stabilizes the Z-geometry of the C3-C4 double bond is the hydrogen bond between the N-H and methoxycarbonyl group.

Table 1. Selected geometric parameters for compound (**2 a**).

Bond lengths (°A)		Bond angles (°)		Torsion angles (°)	
C(1)-S(1)	1.637(4)	C(1)-N(1)-C(3)	129.7 (4)	S(1)-C(1)-C(14)-C(19)	13.8(6)
N(1)-C(1)	1.352(6)	C(1)-N(1)-H(1)	122.1(4)	N(1)-C(1)-C(14)-C(15)	10.4(6)
N(1)-C(3)	1.392(5)	C(3)-N(1)-H(1)	106.2(4)	C(1)-N(1)-C(3)-C(4)	145.6(5)
C(3)-C(4)	1.355(7)	S(1)-C(1)-N(1)	125.0(3)	N(1)-C(3)-C(8)-C(9)	-45.4(6)
		S(1)-C(1)-C(14)	121.3(3)	C(4)-C(3)-C(8)-C(9)	128.7(5)
		N(1)-C(1)-C(14)	113.6(4)	C(3)-C(4)-C(6)-O(1)	18.4(7)

By refluxing **2 a** in methanol we obtained 5-methoxycarbonyl-2,6-diphenyl-4-thioxo-3,4-dihydropyrimidine (**3**). The cyclization process entails an inversion of the geometry of the C3-C4 double bond.

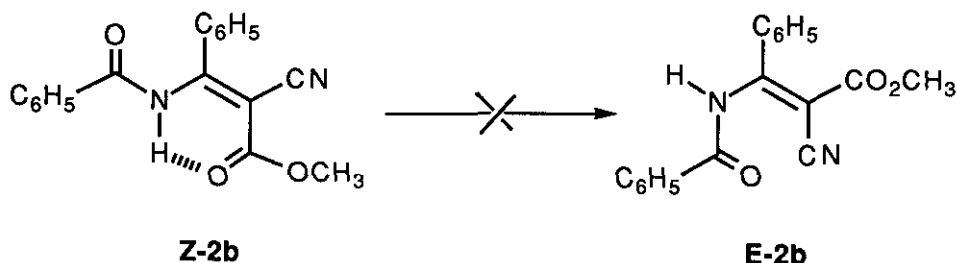
Scheme 3



Under the same conditions the Michael adduct (**2 b**) does not undergo cyclization but yields

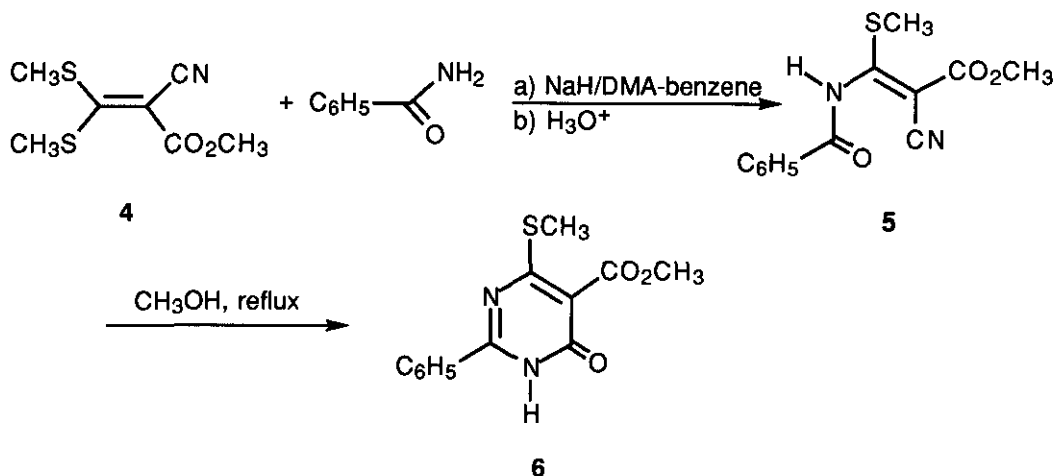
methyl 3-amino-2-cyano-3-phenylpropenoate as described in the literature.⁵ This result can be explained by stabilization of the Z configuration owing to the hydrogen bond between the N-H and C=O groups.

Scheme 4

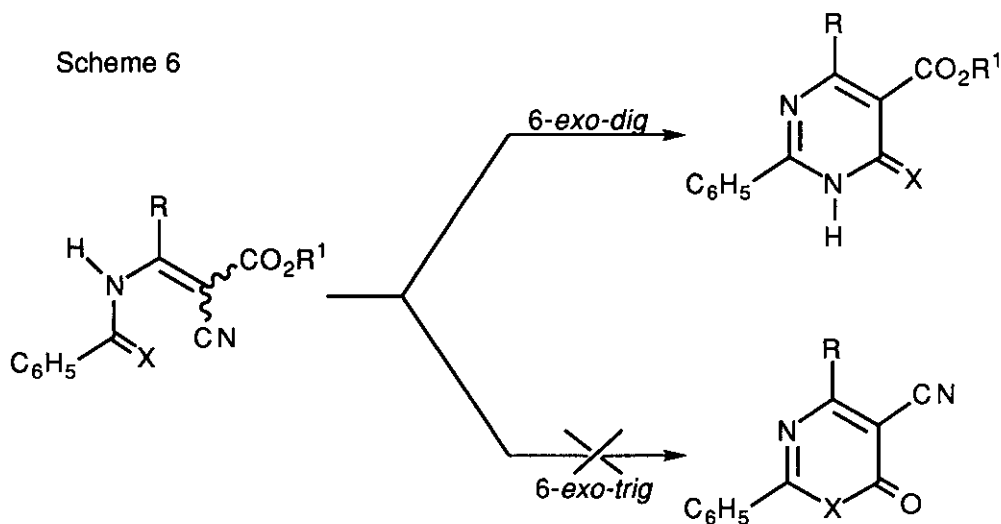


In a previous paper,⁴ we described the synthesis of 5-methoxycarbonyl-6-methylthio-2-phenyl-4-thioxo-3,4-dihydropyrimidine from methyl 3,3-bis(methylthio)-2-cyanopropenoate (**4**) and thiobenzamide by *in situ* cyclization of the intermediate. Under similar conditions the reaction of methyl 3,3-bis(methylthio)-2-cyanopropenoate (**4**) with benzamide affords methyl 3-benzamido-2-cyano-3-methylthiopropenoate (**5**). The Z geometry of the carbon-carbon double bond was established from NOE experiments and is the opposite to that found in the adduct (**2b**). This can be explained by an attractive nonbonded S...O=C interaction such as that found in related compounds.⁶ Treatment of **5** in methanol at reflux affords 5-methoxycarbonyl-6-methylthio-4-oxo-2-phenyl-3,4-dihydropyrimidine (**6**).

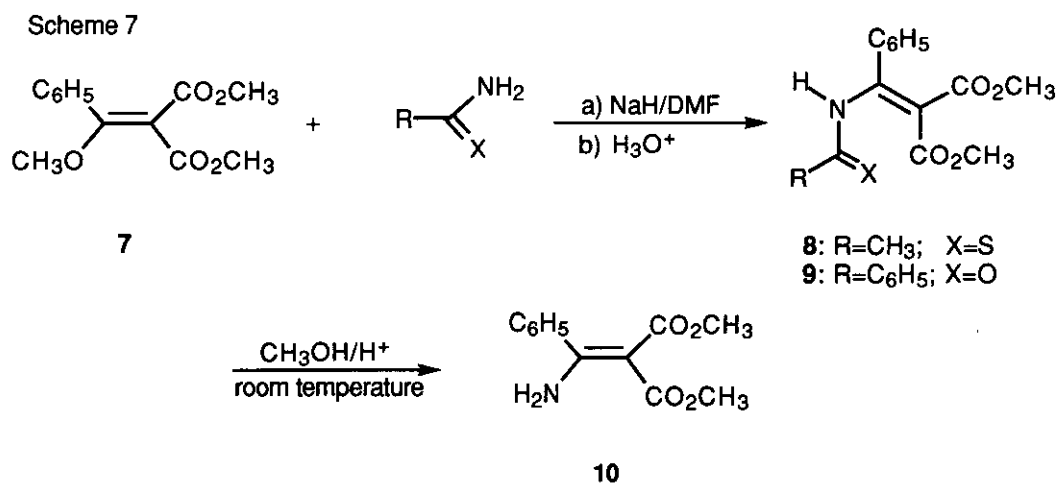
Scheme 5



In all cases studied two alternative cyclizations are possible, though only 5-alkoxycarbonyl-4-thioxo(or 4-oxo)-3,4-dihydropyrimidines formed by a 6-*exo-dig* process were obtained. These results suggest that heterocyclization is controlled by stereoelectronic factors. The rigidity of the chain restricts the relative motion of the terminal groups and precludes the attack of the sulphur (or oxygen) above or below the carbonyl group. On the contrary, the nucleophile can attack the cyano function with a trajectory⁷ having an SCN angle of *ca.* 120° without distortion of the chain.



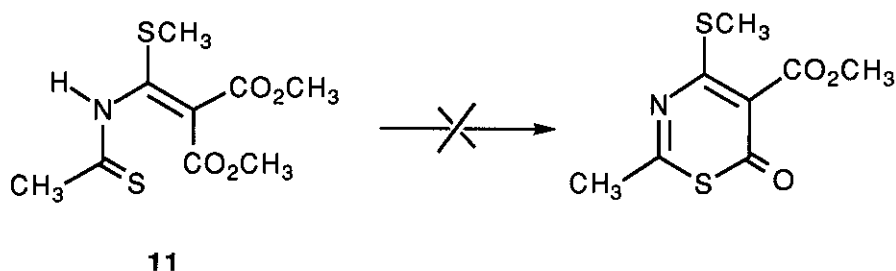
In order to assess this assumption we carried out the synthesis of dimethyl 1-phenylmethylenemalonates (**8**) and (**9**). By refluxing **8** or **9** in methanol, unchanged starting materials were recovered whereas by stirring with sulfuric acid at room temperature dimethyl 1-amino-1-phenylmethylenemalonate (**10**) was isolated in both cases.



Spectroscopic and physical data of **10** are in agreement with those previously reported.⁸

Likewise dimethyl 1-methylthio-1-thioacetamidomethylenemalonate (**11**) obtained from thioacetamide and dimethyl bis(methylthio)methylenemalonate does not cyclize in methanol at reflux.

Scheme 8

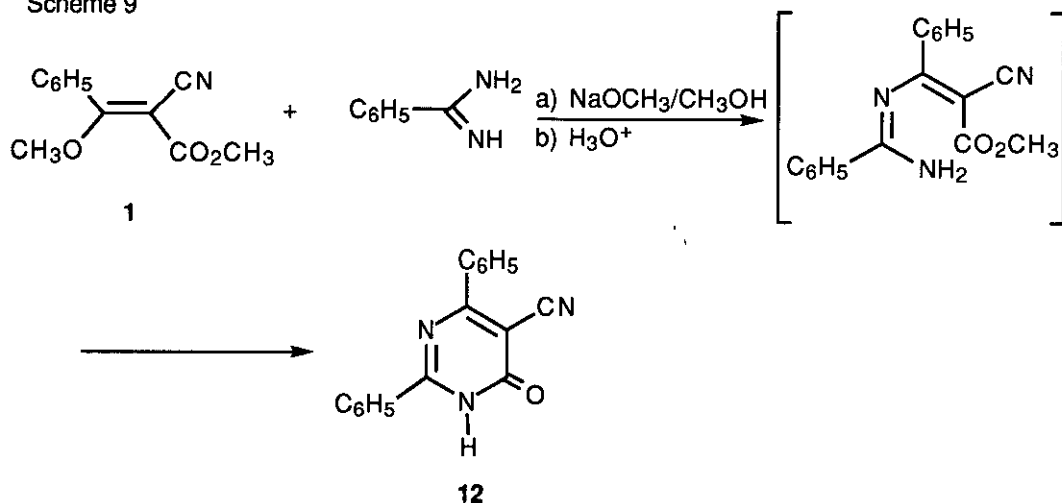


These facts are additional proof of the stereoelectronic control in the cyclization of the condensation products obtained from amides or thioamides and alkoxyethylene compounds or ketene dithioacetals.

SYNTHESIS OF PYRIMIDINES FROM BENZAMIDINE OR THIOUREA

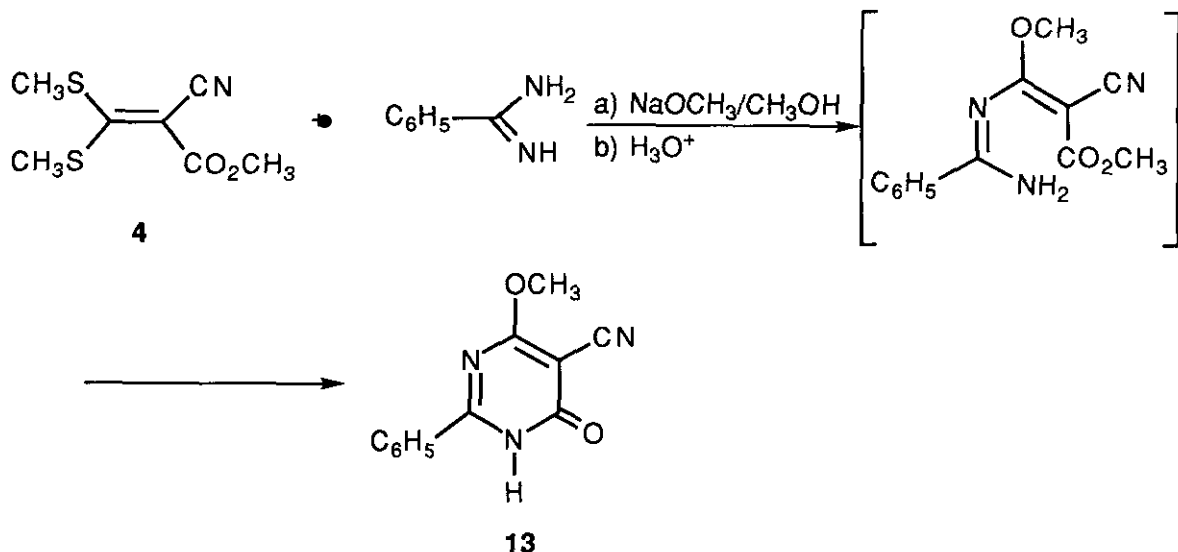
The literature describes several regioselective cyclizations of adducts resulting from addition of amidines to methoxymethylene compounds,^{9,10} ketene dithioacetals¹¹ and ketene *S,N*-acetals.¹² With the objective to study in depth the regioselectivity of these processes, we carried out the reaction of the methoxymethylene compound (**1**) with benzamidine, which afforded 5-cyano-4-oxo-2,6-diphenyl-3,4-dihydropyrimidine (**12**) as the sole product of the reaction.

Scheme 9



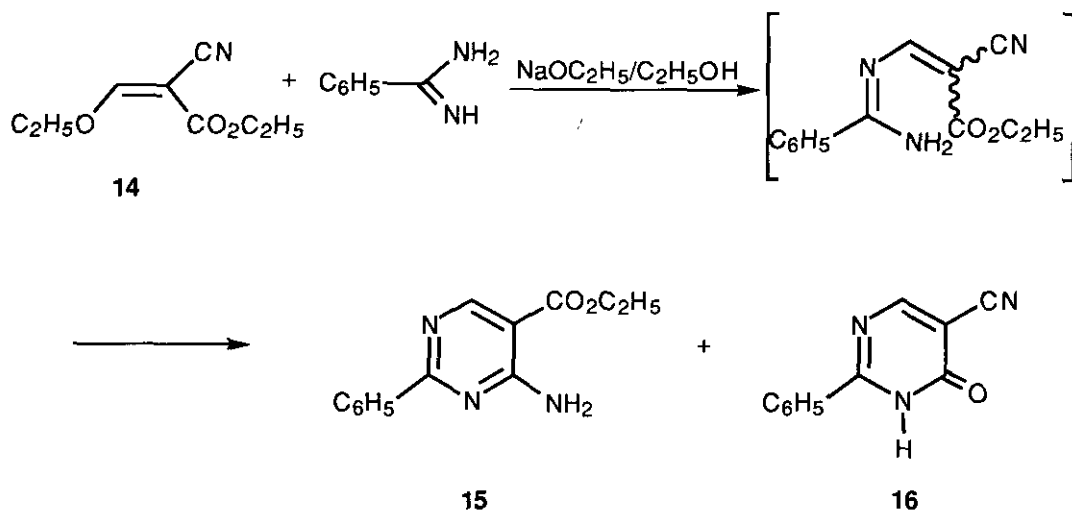
Analogous results were obtained when ketene dithioacetal (**4**) was reacted with benzamidine.

Scheme 10



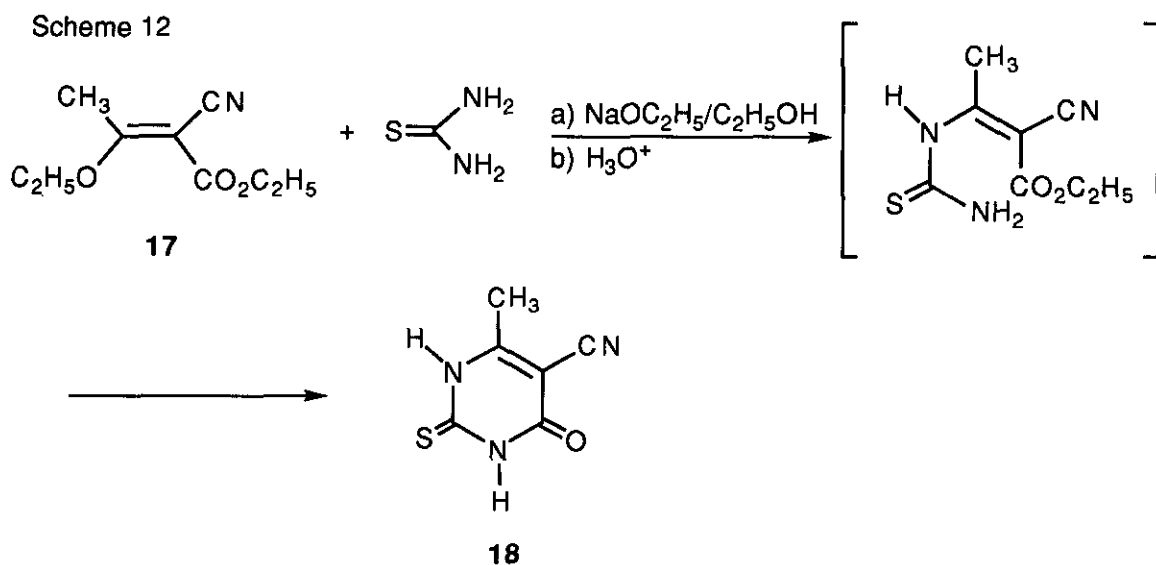
On the contrary, the reaction of ethyl 2-cyano-3-ethoxypropenoate (**14**) with benzamidine yields a mixture of the pyrimidines (**15**) and (**16**) resulting from the cyclization at the cyano and ethoxycarbonyl group respectively.

Scheme 11



The reaction of thioureas with alkyl benzylidenecyanoacetates affords a route to the synthesis of 2-thiodiuracils.¹³ S. Kambe *et al.*¹⁴ described the synthesis of 2-thiouracils from

alkoxymethylene compounds and thiourea. Now we report the synthesis of 5-cyano-6-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (**18**) from thiourea and ethyl 2-cyano-3-ethoxybutenoate (**17**) by regioselective cyclization at the alkoxycarbonyl group.



These results are at variance with those described in the literature¹⁵ concerning the reaction of thiourea with ethyl 2-cyano-3-ethoxypropenoate, which yields the 4-amino-5-ethoxycarbonyl-2-thioxo-1,2-dihydropyrimidine as the major product of the reaction.

From these results and the ones obtained from the reaction with benzamidine, we can conclude that the regioselectivity of the cyclization in these processes is not controlled by stereoelectronic factors but rather from the geometry of the carbon-carbon double bond of the intermediate. The steric hindrance between the phenyl (or methyl) and the ethoxycarbonyl functions favors the Z-configuration of the intermediary condensation products and subsequent cyclization with this group to afford the corresponding 4-oxopyrimidine.

EXPERIMENTAL

All melting points were determined on a Büchi SMP-20 or Electrothermal IA 6304 (for mps above 260 °C) and are uncorrected. Ir spectra were recorded on a Perkin Elmer 883 spectrophotometer. Nmr spectra were performed on a Varian Unity at 300 MHz. Mass spectra were obtained on a Hewlett Packard HP-5988 at 70eV. Microanalyses were performed on a Perkin Elmer 240. Flash

column chromatography was carried out on silica gel SDS 230-400 mesh.

Methyl 3-benzamido-2-cyano-3-methylthiopropenoate (**5**) was obtained according the reported procedure.¹⁶

Methyl (Z)-2-Cyano-3-phenyl-3-thiobenzamidopropenoate (2a): To a stirred suspension of 80% sodium hydride (90 mg, 3 mmol) in dry dimethylformamide (20 ml), thiobenzamide (274 mg, 2 mmol) and methyl 2-cyano-3-methoxy-3-phenylpropenoate (**1**) (434 mg, 2 mmol) were added. The mixture was stirred at room temperature for 7 days and then concentrated to dryness. The residue thus obtained was dissolved in the minimal volume of ethanol and acidified with 2% hydrochloric acid. The solution was extracted with dichloromethane and the combined extracts washed with water. The residue obtained after concentration of the organic extracts was treated with hexane affording a solid which was recrystallized from ethanol. Yield 327 mg (51%); mp 148-150 °C; ir (KBr) ν 3229 (N-H), 2211 (C \equiv N), 1696 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.78 (s, 3H, CO $_2$ CH $_3$), 7.41-7.51 (m, 5H, arom), 7.55-7.87 (m, 5H, arom), 12.20 (s, 1H, NH); ms m/z: 322 (M $^+$, 4%), 264 (26), 263 (100), 121 (46), 105 (17), 77 (31). *Anal.* Calcd for C $_{18}$ H $_{14}$ N $_2$ O $_2$ S: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.20; H, 4.18; N, 8.91.

Methyl (Z)-3-Benzamido-2-cyano-3-phenylpropenoate (2b): To a suspension of 80% sodium hydride (180 mg, 6 mmol) in dry dimethylformamide (20 ml), benzamide (484 mg, 4 mmol) and methyl 2-cyano-3-methoxy-3-phenylpropenoate (**1**) (868 mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 72 h and then the solvent was removed at reduced pressure. The residue thus obtained was dissolved in ice-water and acidified with 10% hydrochloric acid. The precipitate formed was filtered and purified by flash column (diameter: 3 cm) chromatography using hexane-ethyl acetate (1/1, v/v) as eluent. The product obtained was recrystallized from ethanol affording 717 mg (61%) of **2b**; mp 152-153 °C; ir (KBr) ν 3225 (N-H), 2222 (C \equiv N), 1715 (C=O), 1688 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.82 (s, 3H, CO $_2$ CH $_3$), 7.47-7.62 (m, 7H, arom), 7.68-7.72 (m, 1H, arom), 7.93-7.96 (m, 2H, arom), 12.00 (s, 1H, NH); ms m/z: 306 (M $^+$, 16%), 247 (20), 106 (14), 105 (100), 104 (12), 77 (79). *Anal.* Calcd for C $_{18}$ H $_{14}$ N $_2$ O $_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.43; H, 4.81; N, 9.43.

5-Methoxycarbonyl-2,6-diphenyl-4-thioxo-3,4-dihydropyrimidine (3): A solution of **2a** (100 mg, 0.31 mmol) in dry methanol (20 ml) was refluxed for 18 h and the precipitate formed was filtered and recrystallized from 2-propanol affording 54 mg (54%) of **3**; mp 236-237 °C; ir (KBr) ν

3144 (N-H), 1736 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.70 (s, 3H, CO_2CH_3), 7.46-7.66 (m, 6H, arom), 7.70-7.76 (m, 2H, arom), 8.14-8.20 (m, 2H, arom); ms m/z: 323 (M^++1 , 18%), 322 (M^+ , 89), 307 (43), 291 (33), 290 (39), 264 (79), 231 (32), 159 (62), 129 (48), 128 (45), 127 (66), 104 (100), 103 (62), 77 (79). *Anal.* Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.21; H, 4.11; N, 8.93.

Methyl 3-Amino-2-cyano-3-phenylpropenoate: A solution of **2b** (200 mg, 0.68 mmol) in dry methanol (20 ml) was refluxed for 86 h and then concentrated to dryness. The residue thus obtained was purified by flash column (diameter: 2 cm) chromatography using hexane-ethyl acetate (2/1, v/v) as eluent affording a solid which was recrystallized from hexane-ethyl acetate. Yield 65 mg (47%); mp 182-183 $^\circ\text{C}$ (lit.,⁵ 182 $^\circ\text{C}$).

5-Methoxycarbonyl-6-methylthio-4-oxo-2-phenyl-3,4-dihydropyrimidine (6): A solution of **5** (262 mg, 0.95 mmol) in dry methanol (30 ml) was refluxed for 3 days and then the precipitate was filtered. By continuing the reflux for 4 days, an additional amount of product was obtained. Combined solids were recrystallized from ethanol affording 197 mg (75%) of **6**; mp 288-289 $^\circ\text{C}$ (lit.,¹⁶ 285 $^\circ\text{C}$).

Dimethyl 1-Methoxy-1-phenylmethylenemalonate (7): To a mechanically stirred suspension of finely divided sodium (previously melted in xylene) (5.97 g, 0.26 mol) in dry ether (350 ml) and dry methanol (3 ml), dimethyl malonate (29 ml, 0.25 mol) was added dropwise. Subsequently freshly distilled benzoyl chloride (40 ml, 0.345 mol) was allowed to drop into the reaction mixture with stirring, which was then refluxed for 4 h. The reaction mixture was then extracted with water (200 ml) and 3x100 ml of 1N NaOH. The aqueous layer was acidified with 10% hydrochloric acid and extracted with 3x100 ml of ether. The combined extracts were dried over magnesium sulfate and evaporated, affording 31.8 g (54%) of dimethyl benzoylmalonate (tautomeric mixture *carbonylic: enolic ca.*, 80:20) which was recrystallized from hexane; mp 41-42 $^\circ\text{C}$; ir (film): ν 1737 (C=O), 1692 (C=O) cm^{-1} ; ^1H nmr (CDCl_3): δ 3.57 (s, 6/10H, CO_2CH_3), 3.80 (s, 48/10H, CO_2CH_3), 3.87 (s, 6/10H, CO_2CH_3), 5.34 (s, 8/10H, CH), 7.41-7.62 (m, 34/10H, arom), 7.91 (d, $J=7.32$ Hz, 16/10H, arom), 13.37 (s, 2/10H, OH); ms m/z: 236 M (M^+ , 9%), 203 (3), 204 (3), 122 (10), 106 (18), 105 (100), 77 (77).

To a solution of dimethyl benzoylmalonate (15.9 g, 73.6 mmol) in dry ethyl acetate (100 ml) kept in

an ice bath, a solution of diazomethane (prepared from Diazald (26.9 g, 125 mmol)) in ether (250 ml) was added dropwise. The reaction mixture was stirred at room temperature for 12 h and then dried with magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from 2-propanol yielded 6.7 g (37%) of product; mp 96-97 °C; ir (KBr): ν 1720 cm^{-1} ; ^1H nmr (acetone- d_6): δ 3.42 (s, 3H, OCH_3), 3.51 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 7.38-7.40 (m, 2H, arom), 7.47-7.50 (m, 3H, arom); ms m/z: 250 (M^+ , 50%), 219 (93), 191 (100), 161 (27), 159 (20), 151 (51), 129 (45), 105 (58), 103 (19), 102 (76), 91 (19), 89 (19), 77 (49). *Anal.* Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_5$: C, 62.39; H, 5.64. Found: C, 62.50; H, 5.51.

Dimethyl 1-Phenyl-1-thioacetamidomethylenemalonate (8): To a stirred suspension of 80 % sodium hydride (150 mg, 5 mmol) in dry dimethylformamide (30 ml), thioacetamide (300 mg, 4 mmol) and dimethyl 1-methoxy-1-phenylmethylenemalonate (1g, 4 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and then the solvent was removed *in vacuo*. The oily residue thus obtained was dissolved in water cooled to 0 °C and acidulated with 2% hydrochloric acid. By extraction with dichloromethane and purification by flash column (diameter: 3 cm) chromatography using hexane-ethyl acetate (12/1, v/v) as eluent an oily product was obtained which on trituration with hexane affords a solid. Yield 304 mg (26%); mp 86-87 °C (hexane); ir (KBr) ν 3297 (N-H), 1722 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 2.43 (s, 3H, CH_3), 3.47 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 7.41 (s, 5H, arom), 11.35 (br s, 1H, NH); ms m/z: 293 (M^+ , 4%), 234 (100), 202 (64), 133 (29), 129 (36), 105 (39), 104 (25), 102 (22), 89 (21), 77 (40). *Anal.* Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4\text{S}$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.48; H, 5.21; N, 4.41.

Dimethyl 1-Benzamido-1-phenylmethylenemalonate (9): To a suspension of 80% sodium hydride (60 mg, 2 mmol) in dry dimethylformamide (30 ml), benzamide (182 mg, 1.5 mmol) and dimethyl 1-methoxy-1-phenylmethylenemalonate (375 mg, 1.5 mmol) were added. After stirring at room temperature for 24 h the solvent was removed at reduced pressure and the concentrate dissolved in water. Neutralization with 2% hydrochloric acid gave a solid precipitate which was filtered. The filtrate was extracted with dichloromethane and the combined organic phases were washed three times with water, dried over magnesium sulfate and concentrated to dryness affording an additional amount of product. Both fractions of product were purified by flash column (diameter: 3 cm) chromatography with hexane-ethyl acetate (2/1, v/v) as eluent yielding 259 mg (51%) of **9** which was recrystallized from hexane-ethyl acetate; mp 108-109 °C; ir (KBr) ν 3219

(N-H), 1730 (C=O), 1705 (C=O), 1665 (CONH) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.40 (s, 3H, CO_2CH_3), 3.81 (s, 3H, CO_2CH_3), 7.39 (s, 5H, arom), 7.57-7.66 (m, 3H, arom), 7.95-7.98 (m, 2H, arom), 11.80 (s, 1H, NH); ms m/z : 339 (M^+ , 8%), 281 (17), 280 (97), 105 (100), 104 (11), 77 (77). *Anal.* Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.43; H, 5.11; N, 4.33.

Dimethyl 1-Methylthio-3-thioacetamidomethylenemalonate (11): To a suspension of 80% sodium hydride (240 mg, 8 mmol) in dry dimethylformamide (30 ml), thioacetamide (300 mg, 4 mmol) and dimethyl bis(methylthio)methylenemalonate (945 mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 72 h and then the solvent was removed *in vacuo*. The residue thus obtained was dissolved in water, acidified at 0 °C with 2% hydrochloric acid and extracted with dichloromethane. The residue obtained by concentration of the combined organic extracts was purified by flash column (diameter: 3 cm) chromatography using hexane-ethyl acetate (2/1, v/v) as eluent. The oily product obtained was triturated with hexane-ethyl acetate affording a solid which was recrystallized from ethyl acetate. Yield 263 mg (25%); mp 129-131 °C; ir (KBr) ν 3190 (N-H), 1708 (C=O) cm^{-1} ; ^1H nmr (acetone- d_6): δ 2.33 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 3.68 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 10.45 (s, 1H, NH); ms (CI) m/z : 264 (M^++1 , 96%), 248 (117), 234 (11), 233 (11), 232 (100), 218 (15), 216 (17), 200 (20), 158 (12), 89 (92). *Anal.* Calcd for $\text{C}_9\text{H}_{13}\text{NO}_4\text{S}_2$: C, 41.05; H, 4.98; N, 5.32. Found: C, 41.26; H, 4.73; N, 5.71.

5-Cyano-4-oxo-2,6-diphenyl-3,4-dihydropyrimidine (12): To a solution of sodium (100 mg, 4.35 mmol) in dry methanol (40 ml), methyl 2-cyano-3-methoxy-3-phenylpropenoate (**1**) (434 mg, 2 mmol) and benzamidine hydrochloride (313 mg, 2 mmol) were added. After 48 h stirring at room temperature the reaction mixture was poured into ice-water (200 ml) and neutralized with 10% hydrochloric acid. The colorless precipitate was filtered and recrystallized from methanol affording 382 mg (70%) of **12**; mp 350-354°C (lit.,¹⁷ 350-356 °C).

5-Cyano-6-methoxy-4-oxo-2-phenyl-3,4-dihydropyrimidine (13): To a solution of sodium (40 mg, 1.74 mmol) in dry methanol (40 ml), methyl 3,3-bis(methylthio)-2-cyanopropenoate (157 mg, 0.77 mmol) and benzamidine hydrochloride (156 mg, 0.77 mmol) were added. The reaction mixture was stirred at room temperature for 5 h and then concentrated to dryness. The resulting residue was treated with water (40 ml) and the solution acidified with 20% hydrochloric acid affording a colorless solid which was recrystallized from methanol yielding 106 mg (61%) of **13**;

mp 280-281°C; ir (KBr) ν 3419 (N-H), 2223 (C \equiv N), 1660 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 4.11 (s, 3H, OCH $_3$), 7.54-7.68 (m, 3H, arom), 8.18-8.22 (m, 2H, arom), 13.5 (br s, 1H, NH); ms m/z 228 ($\text{M}^+ + 1$, 15%), 227 (M^+ , 93), 226 (29), 198 (15), 169 (6), 144 (20), 104 (100), 77 (32). *Anal.* Calcd for C $_{12}$ H $_9$ N $_3$ O $_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.27; H, 4.11; N, 18.70.

Reactivity of Ethyl 2-Cyano-3-ethoxypropenoate (14) with Benzamidine. Synthesis of 15 and 16: To a solution of sodium (184 mg, 4 mmol) in dry ethanol (40 ml), **14** (644 mg, 4 mmol) and benzamidine hydrochloride (626 mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and then the solvent was removed *in vacuo*. The resulting residue was treated with water (70 ml) broken up in an ultrasonic bath and filtered yielding 210 mg (22%) of **15**; mp 115-116 °C (hexane) (lit.,¹⁸ 115 °C).

The filtrate was acidified with 10% hydrochloric acid affording a colorless precipitate which was filtered and recrystallized from methanol yielding 240 mg (31%) of **16**; mp 302-304 °C (lit.,¹⁸ > 300 °C).

5-Cyano-6-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (18): To a solution of sodium ethoxide in dry ethanol (40 ml) prepared from sodium (92 mg, 4 mmol), thiourea (305 mg, 4 mmol) and ethyl 2-cyano-3-ethoxybutenoate (**17**) (732 mg, 4 mmol) were added. The reaction mixture was refluxed for 2.5 h and then concentrated to dryness. The residue thus obtained was dissolved in ice-water and neutralized with 5% acetic acid. The precipitate formed was filtered and recrystallized from 50% acetic acid affording 550 mg (82%) of **18**; mp 270-272 °C; ir (KBr) ν 3519 and 3435 (N-H), 2238 (C \equiv N), 1661 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 2.29 (s, 3H, CH $_3$), 11.80 (br s, 2H, NH); ms m/z 168 ($\text{M}^+ + 1$, 12%), 167 (M^+ , 100), 109 (44), 108 (12), 68 (10), 67 (12), 59 (13). *Anal.* Calcd for C $_6$ H $_5$ N $_3$ OS: C, 43.11; H, 3.01; N, 25.13. Found: C, 43.33; H, 3.11; N, 24.87.

X-Ray crystallography

Crystallographic and experimental details for the X-Ray crystal structure determination are given in Table 2. Data were collected at room temperature. Intensities were corrected for Lorentz polarization effects in the usual manner. No absorption or extinction corrections were made. The structure was solved by a combination of direct methods and Fourier synthesis.

The structure of compound **2a** was refined on F by full-matrix least-squares calculations. All the non-hydrogen atoms were refined anisotropically. In the later stages of refinement the hydrogen

atoms were included in calculated positions with thermal parameters equivalent to those of the atoms to which they are attached, and in the last cycle of refinement their parameters were fixed. Final values of $R = 0.079$ and $R_w = 0.065$ (non-Poisson weighting scheme for all observed reflections) were obtained.

Anomalous dispersion corrections and atomic scattering factors were taken from International Tables.¹⁹ Calculations were performed with the SDP package²⁰ and the programs MULTAN²¹ and DIRDIF²² on a Microvax II computer.

Table 2. Crystal and X-Ray structural analysis data for compound (**2 a**).

Empirical formula	C ₁₈ H ₁₄ N ₂ O ₂ S
Molecular weight	322.39
Crystal colour/habit	Red; Prism
Crystal system; Space group	Monoclinic; P2 ₁ /c
Unit cell determination	Least squares fit from 25 reflections $\theta < 12^\circ$
a, b, c (°A)	9.172(2), 8.405(1), 20.678(4)
β (deg)	91.44(1)
U/ °A ³ , Z	1593.6(4), 4
D_c / gcm ⁻³	1.344
μ (Mo-K α)/cm ⁻¹	2.04
F(000)	672
Technique.	Four circle diffractometer; bisecting geometry, graphite oriented monochromator. ω - θ scan mode.
θ range.	$2 \leq \theta \leq 27$
Reflections measured	3940
Observed reflections [$I > 2\sigma(I)$]	1631
Unique reflections	1598
Range of hkl	$0 < h < 11$, $0 < k < 10$, $-26 < l < 26$
Standard reflections	2 every 120 minutes; no variation.
Number of parameters refined	209
Goodness of fit	1.626
R	0.079
R _w	0.065

Weighting scheme	$w=4F^2/\sigma(F^2)^2; \sigma(F^2)=[\sigma(I)^2+(0.04F^2)^2]$
Max. peak in final diff.map.	0.362 e ^o A ⁻³
Min. peak in final diff.map.	-0.462 e ^o A ⁻³

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