SYNTHESIS OF NITROGEN HETEROCYCLES FROM 1-METHYLTHIO-2-PHENYL-2-AZABUTA-1,3-DIENE-4,4-DICARBONITRILES

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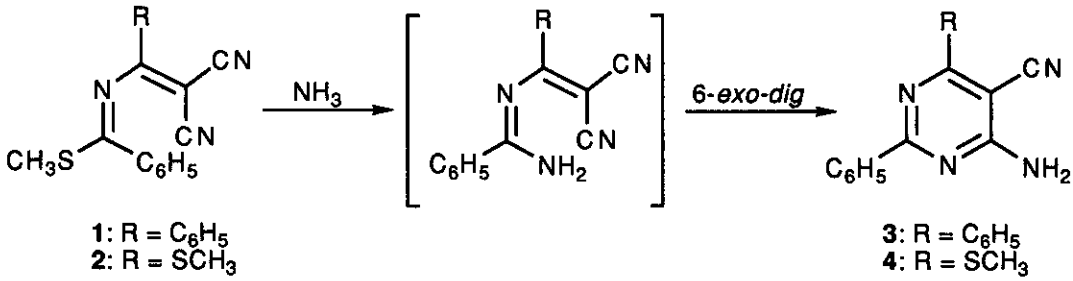
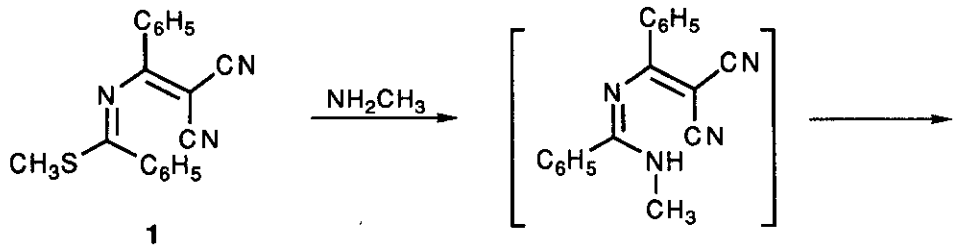
Abstract- The reactions of tittle compounds with different nucleophiles afforded a simple method for a synthesis of pyrimidines, 1,2,4-triazoles, 1,2,4-oxadiazoles and 1,3,5-triazines.

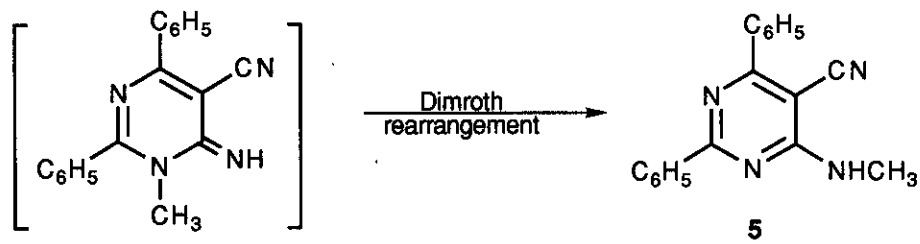
The utility of thioimidates in the synthesis of heterocyclic compounds has been very studied.[1-13] Thus cyclic or acyclic thioimidates with ketenes[1,2] or acid chlorides[3-5] afford β-lactams. Substituted 1,2,4-triazoles have been obtained from reaction of thioimidates with hydrazines,[6] hydrazides[7] or amidrazones.[8] Imidazoles,[9] thiazoles,[10] thiazafosfoles[11] and thiophenes[12] have also been synthetized from thioimidates. Howewer, the use of *N*-alkenylthioimidates to a synthesis of heterocycles is more scarce. In the literature[3,13] the formation of β-lactams from *N*-alkenyl-thioimidates has been described. In a previous paper[14] we described the synthesis of 1-methylthio-2-azabuta-1,3-diene-4-carbonitriles from thioamides and methoxymethylene compounds or ketene dithioacetals. In this paper we report the reactivity of the 1-methylthio-1-phenyl-2-azabuta-1,3-diene-4,4-dicarbonitriles (**1**) and (**2**) with nitrogen nucleophiles which affords different heterocyclic systems.

SYNTHESIS OF 4-AMINOPYRIMIDINES

The reactions of 2-azabuta-1,3-dienes (**1**) and (**2**) with ammonia or methylamine afforded 4-aminopyrimidines (**3-5**) according the following process.



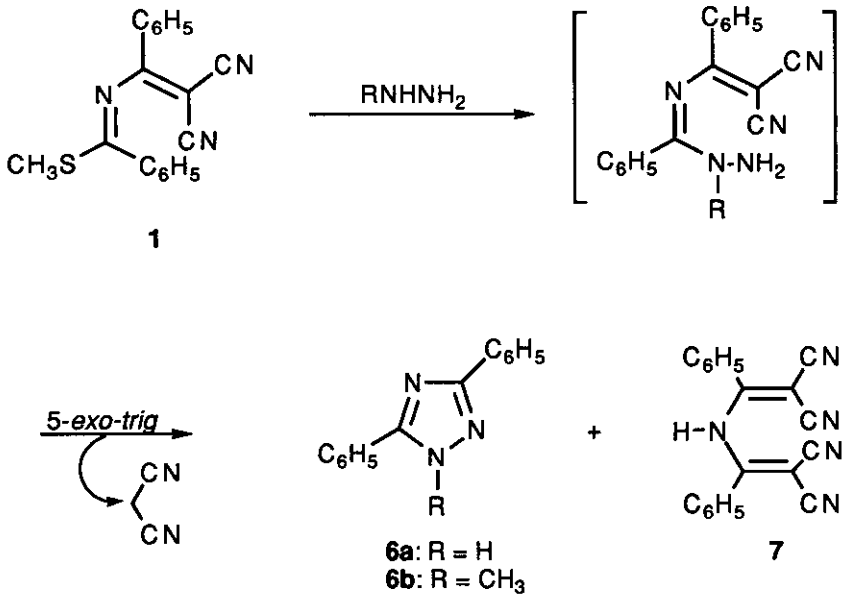




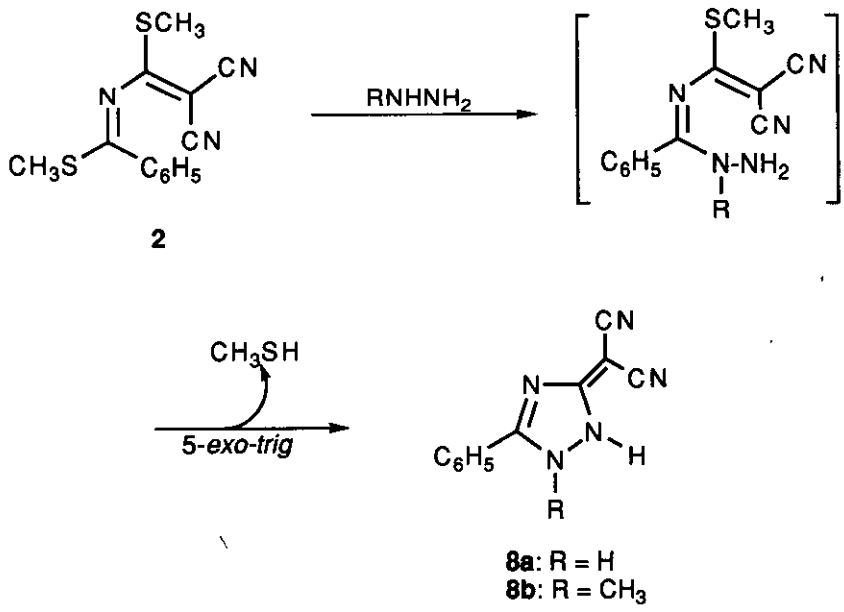
The formation of the 4-methylaminopyrimidine (**5**) can be explained by Dimroth rearrangement of the iminopyrimidine initially formed. The structure of the rearranged product was established from spectroscopic data and particularly from the coupling (J = 3 Hz) between N-H and methyl group.

SYNTHESIS OF 1,2,4-TRIAZOLES AND 1,2,4-OXADIAZOLES

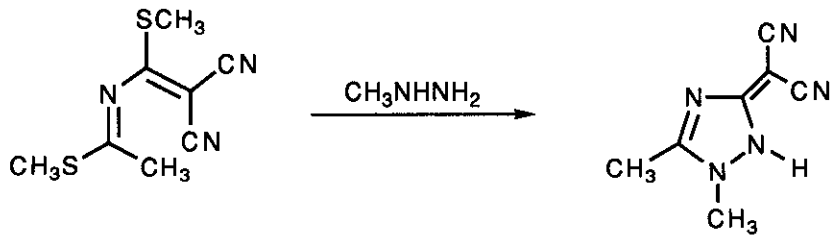
3,5-Diphenyl-1,2,4-triazoles.- The reactions of *(E)-1-methylthio-1,3-diphenyl-2-azabuta-1,3-diene-4,4-dicarbonitrile* (**1**) with hydrazines yield the corresponding 3,5-diphenyl-1,2,4-triazole (**6**). Besides 1,2,4-triazole (**6**) in both cases a by-product was obtained which was identified as the *bis(2,2-dicyano-1-phenylethenyl)amine* (**7**). This product was formed by addition of malononitrile to the 2-azabuta-1,3-diene (**1**).



3-Dicyanomethylene-5-phenyl-1,2,4-triazoles.- We have also studied the reactivity of the *(E)-1,3-dimethylthio-1-phenyl-2-azabuta-1,3-diene-4,4-dicarbonitrile* (**2**) with hydrazines which yield the 3-dicyanomethylene-1,2,4-triazoles (**8**).

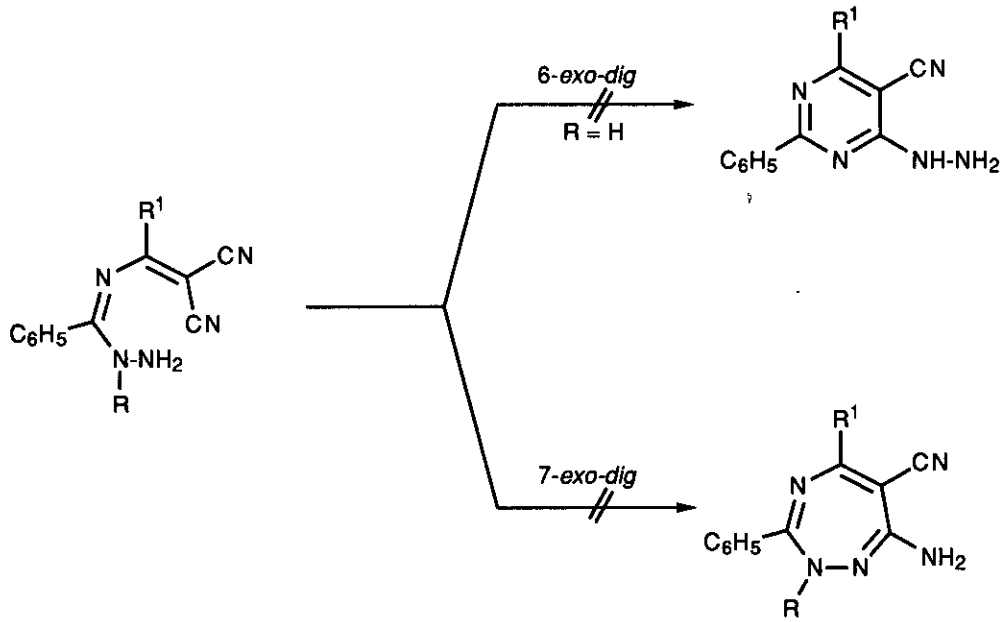


The reaction of **2** with methylhydrazine may occur in either of two orientations to yield either triazole (**8b**) or its isomer. The proposed structure (**8b**) assumes attack on the imidic carbon by the more nucleophilic secondary amino group. In order to asses this assumption we have synthesized the *3-dicyanomethylene-1,5-dimethyl-2,3-dihydro-1,2,4-triazole* (**10**) from the 2-azabuta-1,3-diene-4,4-dicarbonitrile (**9**) and methylhydrazine. The vicinity of methyl groups in the 1,2,4-triazole (**10**) was established from NOE experiments by irradiation of both methyl groups.

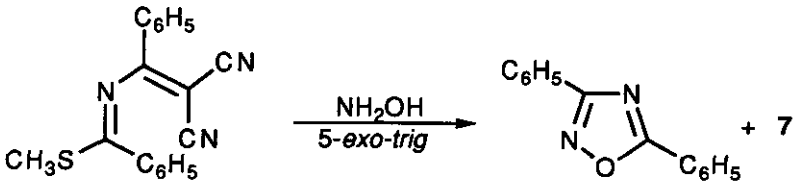


9 **10**

Besides the 5-*exo-trig* process two other cyclizations are possible, depending upon the nitrogen involved in the attack. The first one leading to a 4-hydrazinopyrimidine is a 6-*exo-dig* process and a second route leading to a 1,2,4-triazepine is a 7-*exo-dig* cyclization. These processes are favoured according to the Baldwin rules,[15] howewer, we have not isolated any of these products.



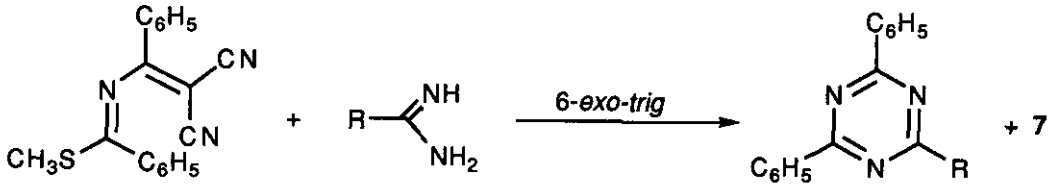
3,5-Diphenyl-1,2,4-oxadiazole.- In the same fashion the reaction of **1** with hydroxylamine afforded the *3,5-diphenyl-1,2,4-oxadiazole* (**11**) besides the amine (**7**) as a by-product of the reaction.



1 **11**

SYNTHESIS OF 1,3,5-TRIAZINES

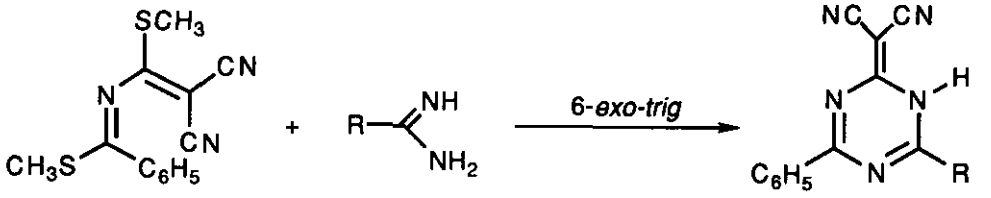
The reactions of amidines or guanidine with the 2-azabuta-1,3-diene (**1**) provided a simple method for the synthesis of trisubstituted 1,3,5-triazines (**12**) through a 6-*exo-trig* cyclization process.



1

12a: R =CH_3
12b: R =C_6H_5
12c: R = NH_2

Similarly, the reactions of **2** with amidines or guanidine afforded the 2-dicyanomethylene-1,3,5-triazines (**13**).



2

13a: R = CH_3
13b: R = C_6H_5
13c: R = NH_2

In all cases studied the intermediate obtained by addition of the amidine to the 2-azabuta-1,3-diene **1** or **2** cyclizes through a 6-*exo-trig* process without isolation of the pyrimidine which could be obtained by a 6-*exo-dig* ring closure. The exclusive formation of 1,3,5-triazines (**1 2**) or (**1 3**) can be explained by the lower nucleophilicity of the nitrogen involved in the 6-*exo-dig* cyclization.

EXPERIMENTAL

All melting points were determined with 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 FT-80 A at 80 MHz. The NOE spectra were registered on a Varian Unity at 300 MHz. Mass spectra were obtained with a Hewlett Packard HP-5988 at 70eV. Microanalyses were performed in a Perkin Elmer 240. Flash column chromatographies were carried out on silica gel SDS 230-400 mesh. 1-Methylthio-2-azabuta-1,3-diene-4,4-dicarbonitriles (**1**, **2** and **9**) were obtained according reported procedure.[14]

4-Amino-5-cyano-2,6-diphenylpyrimidine (**3**): To a mixture of 2-propanol (10 ml) and 28 Be° ammonia (10 ml, 167 mmol), a solution of **1** (303 mg, 1 mmol) in 2-propanol (60 ml) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. The precipitate formed was filtered and the mother liquors were concentrated *in vacuo*. Treatment of the residue with water afforded an additional amount of product which was purified by flash column (diameter: 3 cm) chromatography on silica gel using hexane-ethyl acetate (5/1, v/v) as eluent and recrystallized from acetonitrile. Yield 128 mg (47 %); mp 210-211 °C (lit.,[16] 209-211 °C).

4-Amino-5-cyano-6-methylthio-2-phenylpyrimidine (**4**): To a solution of **2** (273 mg, 1 mmol) in 2-propanol (30 ml), 28 Be° ammonia (20 ml, 335 mmol) was added. The reaction mixture was stirred at room temperature for 5 days and then the solvent was removed at reduced pressure. The solid thus obtained was purified by flash column (diameter: 3 cm) chromatography on silica gel with hexane-ethyl acetate (5/1, v/v) as eluent to afford **4** (213 mg, 88%); mp 179-180 °C (ethanol) (lit.,[17] 180-182 °C).

5-Cyano-4-methylamino-2,6-diphenylpyrimidine (**5**): To a stirred solution of **1** (303 mg, 1 mmol) in methanol (30 ml) a 30% aqueous solution of methylamine (2 ml, 17.4 mmol) was added. The mixture was maintained with stirring for 24 h and then poured into water. The precipitate formed was filtered and recrystallized from methanol affording 252 mg (88%) of **5**; mp 219-220 °C

(lit.,[18] 221-222 °C).

3,5-Diphenyl-1,2,4-triazole (**6a**): To a solution of 100% hydrazine hydrate (398 μl, 8.2 mmol) in methanol (10 ml) a solution of **1** (303 mg, 1 mmol) in methanol (70 ml) was added dropwise. The reaction mixture was stirred at room temperature for 14 h and then concentrated up to dryness. The residue thus obtained was treated with water affording a solid which was filtered and recrystallized fron methanol affording 157 mg (75%) of **6a**; mp 190-191 °C (lit.,[19] 191.5-192.5).
The mother liquors were acidified with 2% hydrochloric acid yielding a precipitate which was collected and recrystallized from ethanol-water affording 48 mg (15%) of **7**; mp 268-270 °C; ir (KBr) υ 3200 (N-H), 2220 (C≡N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.10 (s, 1H, NH), 7.30 (s, 10H arom); ms m/z: 321 (M^+, 24), 320(9), 295(9), 256(28), 244(5), 218(9), 153(86), 127(14), 126(54), 114(8), 104(36), 102(12), 100(17), 99(13), 77(100). *Anal.* Calcd for $C_{20}H_{11}N_5$: C, 74.76; H, 3.45; N, 21.79. Found: C, 74.90; H, 3.35; N, 21.61.

Bis-(2,2-dicyano-1-phenylethenyl)amine (**7**): To a solution of sodium (46 mg, 2 mmol) in dry 2-propanol (60 ml), malononitrile (66 mg, 1 mmol) and **1** (303 mg, 1 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and then the solvent was removed *in vacuo*. The solid thus obtained was dissolved in water and acidulated with 2% hydrochloric acid affording a precipitate which was collected and recrystallized from ethanol-water yielding 298 mg (93%) of **7**.

1-Methyl-3,5-diphenyl-1,2,4-triazole (**6b**): A solution of **1** (303 mg, 1 mmol) in methanol (70 ml) was added dropwise to a mixture of methylhydrazine (392 μl, 7.32 mmol) and methanol (10 ml). The reaction mixture was maintained with stirring at room temperature for 2 h and then concentrated up to dryness. The residue thus obtained was treated with water affording a precipitate which was filtered. The aqueous phase was extracted with ether affording an additional amount of product. The combined solids were recrystallized from ethanol-water affording 203 mg (91%) of **6b**; mp 80-81 °C (lit.,[19] 81.5-82.5 °C).
Acidification of the aqueous phase with 2% hydrochloric acid afforded 15 mg (5%) of **7**.

3-Dicyanomethylene-5-phenyl-2,3-dihydro-1,2,4-triazole (**8a**): To a mixture of 100% hydrazine hydrate (390 µl, 8 mmol) in 2-propanol (70 ml), 273 mg (1 mmol) of **2** was added. The mixture was stirred at room temperature for 14 h and then concentrated *in vacuo*. The resulting residue was dissolved in water (20 ml) and acidified with 2% hydrochloric acid. The precipitate thus obtained was filtered and purified by recrystallization from methanol affording 120 mg (57%) of **8a**; mp 265-266 °C; ir(KBr) υ 3120(N-H), 2220 and 2176(C≡N) cm^{-1}; ^1H *nmr* (DMSO-d_6): δ 7.51 (br s, 3H arom), 7.93 (br s, 2H arom), 13.55 (br s, 1H, NH); ms m/z 210(M^++1, 13), 209(M^+, 87), 180(6),154(11), 144(8), 118(14), 116(18), 105(11), 104(100), 103(31), 91(10), 77(50). *Anal.* Calcd for $C_{11}H_7N_5$: C, 63.15; H, 3.37; N, 33.48. Found: C, 63.36; H, 3.41; N, 33.31.

3-Dicyanomethylene-1-methyl-5-phenyl-2,3-dihydro-1,2,4-triazole (**8b**): By the same procedure as described in the preceeding case, from 546 mg (2 mmol) of **2** and 75 µl (3 mmol) of methylhydrazine and after 48 h of reaction, 170 mg (38%) of **8b** was obtained which was purified by recrystallization from methanol; mp 211-212 °C; ir (KBr) υ 2201 and 2158 (C≡N) cm^{-1}; ^1H nmr (DMSO-d_6); δ 3.81 (s, 3H, CH_3), 7.34-7.89 (m, 5H arom); ms m/z 224(M^++1, 11), 223(M^+, 76), 222(47), 120(10), 105(12), 104(100), 103(25), 92(13), 77(44). *Anal.* Calcd for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.38. Found: C, 64.70; H, 3.92; N, 31.48.

3-Dicyanomethylene-1,5-dimethyl-2,3-dihydro-1,2,4-triazole (**10**): To a solution of the 2-azabuta-1,3-diene-4,4-dicarbonitrile (**9**) (206 mg, 1 mmol) in 2-propanol (15 ml), methylhydrazine (160 µl, 3 mmol) was added. The reaction mixture was stirred at room temperature for 60 h and then concentrated up to dryness. The residue was treated with water (20 ml) and acidified with 2% hydrochloric acid. By extraction with dichloromethane a crude product was obtained that was purified by recrystallization from 2-propanol to afford 76 mg (47 %) of product; mp 236-237 °C; ir (KBr) υ 2203 and 2164 (C≡N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 3.67 (s, 3H, N-CH_3); ms m/z 162(M^+ +1, 7%), 161(M^+, 73), 121(7), 120(100), 118(20), 94(9), 93(6), 92(30). *Anal.* Calcd for $C_7H_7N_5$: C, 52.17; H, 4.38; N, 43.45. Found: C, 52.05; H, 4.47; N, 43.37.

3,5-Diphenyl-1,2,4-oxadiazole (**11**): To a solution of sodium methoxide (178 mg, 3.3 mmol) in dry methanol (25 ml), hydroxylamine hydrochloride (209 mg, 3 mmol) and **1** (303 mg, 1 mmol) were added. The mixture was stirred at room temperature for 48 h and then poured into water

affording a precipitate which was filtered and recrystallized from methanol; yield 200 mg (90%); mp 106-107 °C (lit.,[19] 108 °C).

By acidification of the aqueous phase with 2% hydrochloric acid 16 mg (5%) of **7** was obtained.

2-Methyl-4,6-diphenyl-1,3,5-triazine (12a): To a suspension of 80% sodium hydride (120 mg, 4 mmol) in dry dimethoxyethane (80 ml), acetamidine hydrochloride (188 mg, 2 mmol) and **1** (303 mg, 1 mmol) were added. The mixture was stirred at room temperature for 24 h and then the solvent was removed *in vacuo*. The resulting residue was treated with water affording a solid which was collected and recrystallized from ethanol-water yielding 115 mg (47%) of **12a**; mp 111-112 °C (lit.,[18] 110-112 °C).

Acidulation of mother liquors with 2% hydrochloric acid afforded 150 mg (47%) of **7**.

2,4,6-Triphenyl-1,3,5-triazine (12b): By the same procedure as described in the preceeding case and after 40 h of reaction 124 mg (40%) of **12b** was obtained which was purified by recrystallization from benzene; mp 236-238 (lit.,[19] 236-237 °C).

The aqueous phase acidified with 2% hydrochloric acid afforded 104 mg (32%) of **7**.

2-Amino-4,6-diphenyl-1,3,5-triazine (12c): To a suspension of 80 % sodium hydride (120 mg, 4 mmol) in dry dimethylformamide (15 ml), guanidine hydrochloride (191 mg, 2 mmol) and **1** (303 mg, 1 mmol) were added. The mixture was stirred at room temperature for 6 h and then concentrated *in vacuo*. The resulting residue was treated with water affording a precipitate which was recrystallized from ethyl acetate yielding 159 mg (64%) of **12c**; mp 170-172 °C (lit.,[20] 168°C).

Acidification of the aqueous phase afforded 92 mg (29%) of **7**.

2-Dicyanomethylene-4-phenyl-1,2-dihydro-1,3,5-triazines 13. General Procedure: To a suspension of 80% sodium hydride (60 mg, 2 mmol) in dry 1,2-dimethoxyethane (50 ml) the corresponding amidine hydrochloride (1 mmol) and **2** (273 mg, 1 mmol) were added. The mixture was stirred at room temperature for 6 days and then concentrated up to dryness. The residue thus obtained was treated with water. The precipitate formed was collected and identified as the starting 2-azabuta-1,3-diene **2**. The filtrate acidulated with 2% hydrochloric acid yielded a solid which was recrystallized from 2-propanol.

2-Dicyanomethylene-6-methyl-4-phenyl-1,2-dihydro-1,3,5-triazine (13a): According to the general procedure 134 mg (57%) of **13a** was obtained which was purified by recrystallization

from 2-propanol; mp 288-290 °C; ir (KBr) υ 3103 (N-H), 2219 (C≡N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 7.39-7.72 (m, 3H arom), 7.86-8.21 (m, 2H arom); ms m/z: 235(M^+, 22), 194(4), 132(9), 129(42), 105(14), 104(100), 103(47), 95(9), 91(15), 77(43). *Anal.* Calcd for $C_{13}H_9N_5$: C, 66.37; H, 3.86; N, 29.77. Found: C, 66.12; H, 3.90; N, 30.01.

2-Dicyanomethylene-4,6-diphenyl-1,2-dihydro-1,3,5-triazine (13b): Following the general procedure 149 mg (50%) of **13b** was obtained; mp 290-292 °C; ir (KBr) υ 3219 and 3108 (N-H), 2217 and 2197 (C≡N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.62 (br s, 6H arom), 7.88-8.65 (m, 4H arom), 10.28 (br s, 1H, NH); ms m/z: 298(M^++1, 21), 297(M^+, 98), 194(7), 130(6), 129(57), 105(8), 104(100), 103(90), 102(8), 91(8), 77(65). *Anal.* Calcd for $C_{18}H_{11}N_5$: C, 72.71; H, 3.73; N, 23.56. Found: C, 72.90; H, 3.65; N, 24.02.

6-Amino-2-dicyanomethylene-4-phenyl-1,2-dihydro-1,3,5-triazine (13c): The solid obtained by treatment with water was a mixture of the 2-azabuta-1,3-diene (**2**) and the 1,3,5-triazine (**13c**). Acidification of aqueous phase affords an additional amount of **13c**. The mixture of **2** and **13c** was purified by flash column (diameter: 3 cm) chromatography using hexane-ethyl acetate (5/1, v/v) as eluent; yield 182 mg (77%); mp > 320 °C; ir (KBr) υ 3457, 3380, 3339, 3215 and 3174 (N-H), 2216 and 2196 (C≡N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.32-7.70 (m, 3H arom), 7.70-8.26 (m, 4H, 2H arom and NH_2); ms m/z 237(M^++1, 6), 236(M^+, 38), 209(3), 181(6), 172(8), 133(32), 129(12), 121(8), 105(34), 104(100), 103(61), 77(62). *Anal.* Calcd for $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.58. Found: C, 61.12; H, 3.50; N, 35.31.

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