Synthetic Studies Using α,β-Unsaturated Nitriles: A One-Step Synthesis of Hexahydropyrimidine Derivatives

Satoshi KAMBE*, Koji SAITO, Masanori HIROSE

Oyama National College of Technology, Oyama-shi, Tochigi, 323, Japan

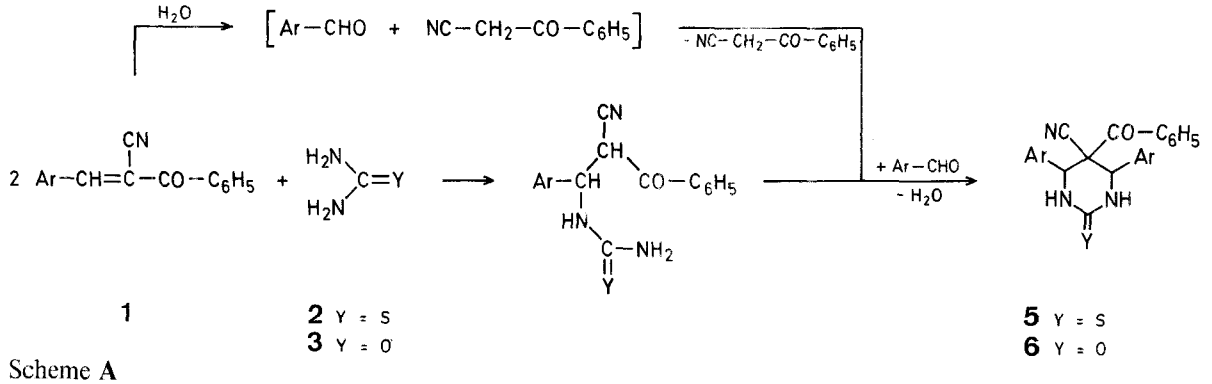
Akio SAKURAI

The Institute of Physical and Chemical Research, Wako-shi, Saitama, 351, Japan

Hiroshi MIDORIKAWA

Department of Domestic Science, Showa Women's University, Tokyo, 154, Japan

α-Benzoylcinnamonitriles **1**, which are easily obtained from aromatic aldehydes and benzoylacetonitrile, are versatile synthetic intermediates for heterocyclic compounds such as 4*H*-pyran[1,2,3] and pyridine[4,5] derivatives. While developing convenient syntheses of heterocyclic compounds utilising α,β-unsaturated nitriles as starting materials, we reported that the nitriles **1** react with mercaptoacetic esters in the presence of triethylamine to give 2-alkoxycarbonyl-5-aryl-4-cyano-3-hydroxy-3-phenyltetrahydrothiophenes[6]. The present paper deals with a one-step synthesis of hitherto un-

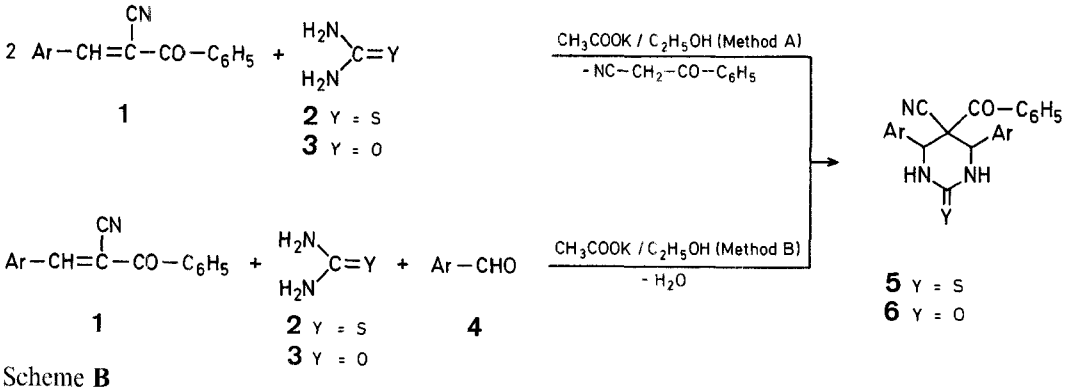


Scheme A

known hexahydropyrimidine derivatives **5** or **6** by the reaction of **1** with thiourea (**2**) or urea (**3**) in the presence of potassium acetate. This method is a development of previously reported synthesis of 4-oxo-2-thioxo-pyrimidines by the ternary condensation of ethyl cyanoacetate, aldehydes and thiourea (**2**)[7].

The reaction of **1** with thiourea (**2**) or urea (**3**) in a 2:1 molar ratio (Method A), carried out in ethanol under reflux in the presence of potassium acetate, affords the thioxo- (**5**) or oxohexahydropyrimidines (**6**), respectively. The same products **5** and **6** are also obtained by the ternary condensation of **1** with thiourea (**2**) or urea (**3**) and an aromatic aldehyde **4** in a molar ratio of 1:1:1 (Method B) in ethanol containing potassium acetate. The products obtained are characterized by microanalysis and spectral data (Table).

We carried out additional reactions to justify the structures of the new products **5** and **6** prepared. Thus, the thioxo compound **5a** is converted to the oxo compound **6a** by oxidation

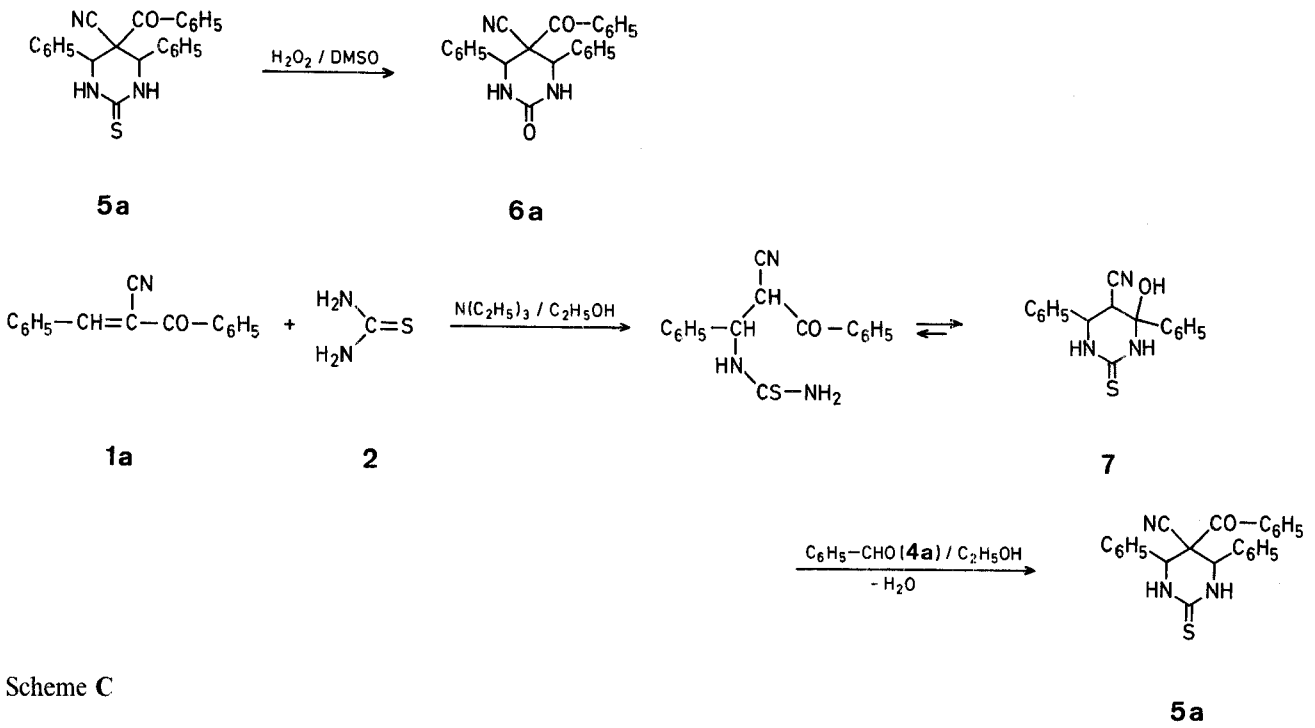


Scheme B

Table. Hexahydropyrimidine derivatives **5** and **6** prepared

Product	Ar	Yield [%] Method A	Yield [%] Method B	m.p. [°C]	Molecular Formula[a]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
5a	C_6H_5	39	43	255–256°	$C_{24}H_{19}N_3OS$ (397.4)	3395, 3150, 2200, 1683	5.50 (s, 2H, CH); 6.45–7.45 (m, 15H$_{arom}$); 9.23 (s, 2H, NH)
5b	4-CH_3—C_6H_4	36	40	253–254°	$C_{26}H_{23}N_3OS$ (425.5)	3375, 3175, 2240, 1550	2.29 (s, 6H, CH_3); 5.40 (s, 2H, CH); 6.13–7.35 (m, 13H$_{arom}$); 9.13 (s, 2H, NH)
5c	4-H_3CO—C_6H_4	5	15	218–219°	$C_{26}H_{23}N_3O_3S$ (457.5)	3400, 3150, 2150, 1663	3.73 (s, 6H, CH_3); 5.30 (s, 2H, CH); 6.55–7.45 (m, 13H$_{arom}$); 8.9 (s, 2H, NH)
5d	4-Cl—C_6H_4	35	45	229–230°	$C_{24}H_{17}Cl_2N_3OS$ (466.3)	3400, 3150, 2150, 1665	5.45 (s, 2H, CH); 6.63–8.10 (m, 13H$_{arom}$); 9.13 (s, 2H, NH)
6a	C_6H_5	27	45	215–216°	$C_{24}H_{19}N_3O_2$ (381.4)	3295, 3175, 2250, 1665	5.40 (s, 2H, CH); 6.45–7.40 (m, 15H$_{arom}$); 7.50 (s, 2H, NH)
6b	4-H_3C—C_6H_4	29	35	235–236°	$C_{26}H_{23}N_3O_2$ (409.5)	3410, 3175, 2210, 1675	2.25 (s, 6H, CH_3); 5.33 (s, 2H, CH); 6.50–7.35 (m, 13H$_{arom}$); 7.43 (s, 2H, NH)
6c	4-H_3CO—C_6H_4	–	7	242–245°	$C_{26}H_{23}N_3O_4$ (441.5)	3370, 3190, 2250, 1700	3.75 (s, 6H, CH_3); 6.30 (s, 2H, CH); 6.85–7.75 (m, 13H$_{arom}$); 8.10 (s, 2H, NH)
6d	4-Cl—C_6H_4	36	53	225–227°	$C_{24}H_{17}Cl_2N_3O_2$ (450.3)	3330, 3175, 2240, 1665	5.40 (s, 2H, CH); 6.70–7.40 (m, 13H$_{arom}$); 8.15 (s, 2H, NH)

[a] Satisfactory microanalyses obtained: C ±0.47, H ±0.05, N ±0.14, S +0.10



Scheme C

with hydrogen peroxide in dimethyl sulfoxide. When the reaction between α-benzoylcinnamonitrile (**1a**) and thiourea (**2**) is carried out in refluxing ethanol containing triethylamine instead of potassium acetate, 4,6-diphenyl-5-cyano-4-hydroxy-2-thioxopyrimidine (**7**) is formed. The reaction of **7** with benzaldehyde in ethanol containing potassium acetate also gives **5a**.

Although an investigation of the reaction mechanism of the Method A was not undertaken, the reaction pathway can be considered to proceed as shown in Scheme **C**.

4,6-Diaryl-5-benzoyl-5-cyano-2-thioxohexahydropyrimidines 5 or 4,6-Diaryl-5-benzoyl-5-cyano-2-oxohexahydropyrimidines 6; General Procedure:

Method A: A mixture of the appropriate α-benzoylcinnamonitrile **1** (10 mmol) and thiourea (**2**; 0.38 g, 5 mmol) or urea (**3**; 0.30 g, 5 mmol) in ethanol (5 ml) containing potassium acetate (0.49 g, 5 mmol) is heated under reflux for 8 h. A crystalline matter precipitates out during the reaction. After cooling the reaction mixture to room temperature the resultant colorless precipitate is collected by suction, washed with water and ethanol. Recrystallization from dimethyl sulfoxide/ethanol gives pure **5** or **6**.

Method B: An equimolar mixture of α-benzoylcinnamonitrile **1** (10 mmol), thiourea (**2**; 0.76 g, 10 mmol) or urea (**3**; 0.60 g, 10 mmol) and aromatic aldehyde **4** (10 mmol) in ethanol (5 ml) containing potassium acetate (0.98 g, 10 mmol) is heated under reflux for 5 h. The mixture is worked up as described in Method A.

Oxidation of 4,6-Diphenyl-5-benzoyl-5-cyano-2-thioxohexahydropyrimidine (5a) to 6a:

4,6-Diphenyl-5-benzoyl-5-cyano-2-thioxohexahydropyrimidine (**5a**; 1.19 g, 3 mmol) is added with stirring to a mixture of dimethyl sulfoxide (5 ml) and 35% hydrogen peroxide (5 ml), and then the mixture is heated at 90–100 °C for 2 h. After cooling to room temperature, the resultant colorless precipitate is collected by suction, washed with water and ethanol. Recrystallization from dimethyl sulfoxide/ethanol gives **6a**; yield: 0.4 g (35%); m.p. 215–216 °C.

4,6-Diphenyl-5-cyano-4-hydroxy-2-thioxopyrimidine (7):

A mixture of α-benzoylcinnamonitrile (**1a**; 2.33 g, 10 mmol) and thiourea **2** (0.76 g, 10 mmol) in ethanol containing a small amount of triethylamine (one drop) is heated under reflux for 20 h. The solid precipitate formed after standing for 24 h at room temperature is collected by suction, washed with water and acetone. Recrystallization from ethanol gives pure **7**; yield: 1.8 g (58%); m.p. 159–160 °C.

$C_{17}H_{15}N_3OS$	calc.	C 66.01	H 4.89	N 13.59	S 10.34
(309.3)	found	66.02	4.75	13.56	10.34

I.R. (Nujol): ν = 3375, 3200, 3180, 2250, 1560 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 3.60 (d, 1H, CH—CN); 4.70 (d, 1H, CH—C_6H_5); 7.40–7.80 (m, 10H_{arom}); 9.20 ppm (s, 2H, NH); (OH not located.

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* To whom correspondence should be addressed.

1 P.H. J. Ooms et al., *Synthesis* **1975**, 260.
2 M. Quinteiro et al., *J. Heterocyclic Chem.* **1978**, 15, 57.
3 M. Quinteiro et al., *Tetrahedron Lett.* **1977**, 1832.
4 M.R.H. Elmoghayar et al., *Synthesis* **1981**, 635.
5 C. Seoane et al., *J. Heterocyclic Chem.* **1981**, 18, 309.
6 S. Kambe et al., *Synthesis* **1980**, 839.
7 S. Kambe et al., *Synthesis* **1979**, 287.