A NOVEL SYNTHESIS OF 1,6-DIHYDRO-2-METHYL-6-OXO[3,4'-BIPYRIDINE]-5-CARBONITRILE (*MILRINONE*)

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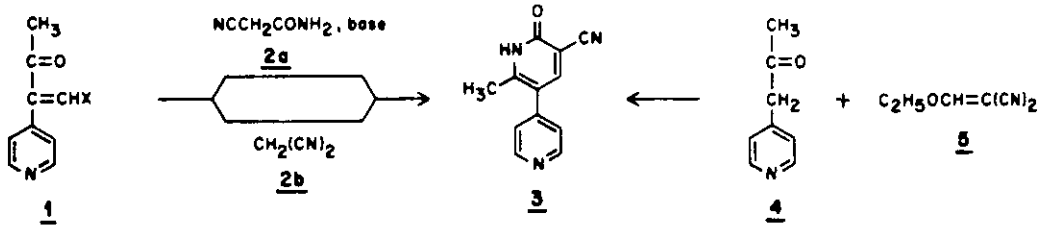
Abstract - Milrinone (3) was prepared either by reacting ethoxymethylenemalononitrile with 1-(4-pyridinyl)-2-propanone or malononitrile with 4-ethoxy-3-(4-pyridinyl)-3-buten-2-one.

Milrinone (3)[1] is a novel cardiotonic agent undergoing clinical investigation. It has been synthesized by the condensation of cyanoacetamide with 4-(dimethylamino)-3-(4-pyridinyl)-3-buten-2-one (1a)[2] or 4-ethoxy-3-(4-pyridinyl)-3-buten-2-one (1b)[3] in the presence of a base. This communication describes the novel preparation of milrinone either by the reaction of 1-(4-pyridinyl)-2-propanone (4) with ethoxymethylenemalononitrile (5) or 4-alkoxy-3-(4-pyridinyl)-3-buten-2-one (1b,c) with malononitrile without the use of an external base.

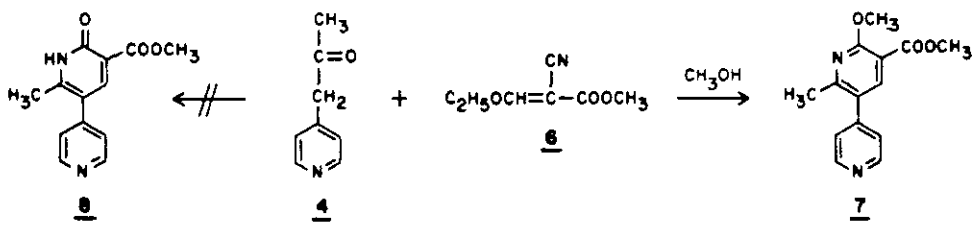


1

a, X = $N(CH_3)_2$
b, X = OC_2H_5
c, X = OCH_3

3

4



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4

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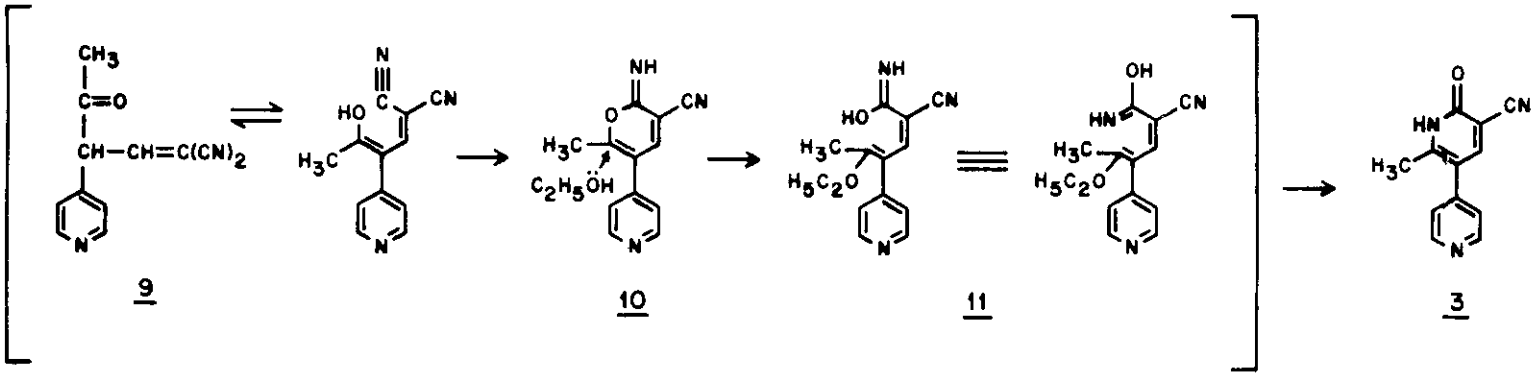
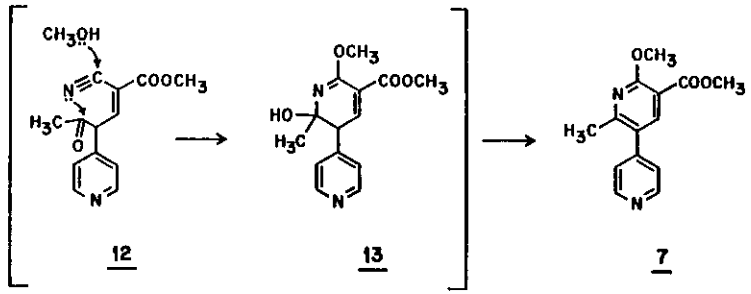


9 10 11 3



12 13 7

When an equimolar mixture of 1-(4-pyridinyl)-2-propanone (4) and ethoxymethylenemalononitrile (5) was heated in ethanol, 1,6-dihydro-2-methyl-6-oxo[3,4'-bipyridine]-5-carbonitrile (3) was obtained in 66% yield. Alternatively, 1-(4-pyridinyl)-2-propanone (4) was first converted to 4-alkoxy-3-(4-pyridinyl)-3-buten-2-ones (1b,c) which were then reacted with malononitrile to give 3 in 65% and 55% yields, respectively. To test the generality of this reaction, 4 was reacted with methyl 2-cyano-3-ethoxy-2-propenoate (6) in methanol. A complex mixture was obtained from which only a small amount of methyl 6-methoxy-2-methyl[3,4'-bipyridine]-5-carboxylate (7) instead of the expected methyl 1,6-dihydro-2-methyl-6-oxo[3,4'-bipyridine]-5-carboxylate (8) was isolated.

Proposed Mechanism - The first step in the reaction between either 1-(4-pyridinyl)-2-propanone (4) and ethoxymethylenemalononitrile (5) or 4-alkoxy-3-(4-pyridinyl)-3-buten-2-one (1b,c) and malononitrile is the formation of an intermediate 9 which may then undergo internal cyclization by nucleophilic attack of oxygen on one of the cyano groups to give an intermediate pyran derivative 10. Nucleophilic attack by ethanol on 10 could lead to ring opening giving 11 which then undergoes ring closure to form 3.

The formation of methyl 6-methoxy-2-methyl[3,4'-bipyridine]-5-carboxylate (7) by the reaction of 1-(4-pyridinyl)-2-propanone (4) with methyl 2-cyano-3-ethoxy-2-propenoate (6) may occur by a ring closure of 12 in a manner different from that of 9. In the case of 12 cyclization takes place by nucleophilic attack of nitrogen on the carbonyl group leading to bipyridine 13 which undergoes dehydration to give 7.

EXPERIMENTAL

1,6-Dihydro-2-methyl-6-oxo[3,4'-bipyridine]-5-carbonitrile (3). (A) A mixture of 13.5 g (0.1 mol) of 1-(4-pyridinyl)-2-propanone (4), 12.2 g (0.1 mol) of ethoxymethylenemalononitrile (5) and 100 ml of ethanol was refluxed with stirring for 5 h and then allowed to cool to room temperature. The light pink crystalline product was filtered, washed with ethanol and dried to yield 14.2 g (66%) of 3, mp >300 °C; ms: m/e 211 (M^+); ^{1}H-nmr (CF_3COOD): δ 12.1 (s, 1H, exchanged), 9.01, 8.23 (AA'BB', 4H, pyridine, J=6 Hz), 8.33 (s, 1H, H-4) and 2.75 (s, 3H, 2-CH_3). Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.14; H, 4.35; N, 20.01.

(B) To a stirred mixture of 60 ml (0.35 mol) of triethyl orthoformate, 55 ml (0.59 mol) of acetic anhydride and 50 ml of acetic acid was added 28.5 g (0.21 mol) of 1-(4-pyridinyl)-2-propanone over a 10 min period whereupon an exothermic reaction took place raising the reaction temperature from 25 to 45 °C. The reaction mixture was further stirred at ambient temperature for 16 h and then concentrated on a rotary evaporator at 70-75 °C to give 69.5 g of a red liquid which was dissolved in 300 ml of ethanol. To this solution was added 13.2 g (0.2 mol) of malononitrile and the resulting reaction mixture was refluxed with stirring for 5 h during which the product

started crystallizing. After the mixture had cooled to room temperature, the product was filtered, washed with ethanol and dried to give 27.5 g (65%) of a light pink solid, mp >300 °C. This product was identical in all respects with the product obtained by process A.

Replacing triethyl orthoformate by trimethyl orthoformate in procedure B gave 3 in 55% yield.

Methyl [6-Methoxy-2-methyl[3,4'-bipyridine]-5-carboxylate (7). A reaction mixture containing 13.5 g (0.1 mol) of 1-(4-pyridinyl)-2-propanone (4), 15.5 g (0.1 mol) of methyl 2-cyano-3-ethoxy-2-propenoate (6) and 250 ml of methanol was stirred and refluxed for 3.5 h to give a red mixture. Removal of methanol gave a red gum. Chromatography (300 g silica gel, 2% methanol in ether) followed by recrystallization from cyclohexane-ether gave 5.2 g (20%) of fluffy tan crystals, mp 136-138 °C; ms: m/e 258 (M^+); ^{1}H-nmr (DMSO-d6): δ 8.65, 7.4 (AA'BB', 4H, pyridine, J=6 Hz), 7.99 (s, 1H, H-4), 4.02 (s, 3H, OCH_3) 3.85 (s, 3H, OCH_3) and 2.49 (s, 3H, 2-CH_3). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.14; H, 5.48; N, 10.80.

ACKNOWLEDGEMENT

The author is grateful to Dr. S.D. Clemans and Mr. A.G. Hlavac for the nmr and ms spectra.

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Received, 18th February, 1985