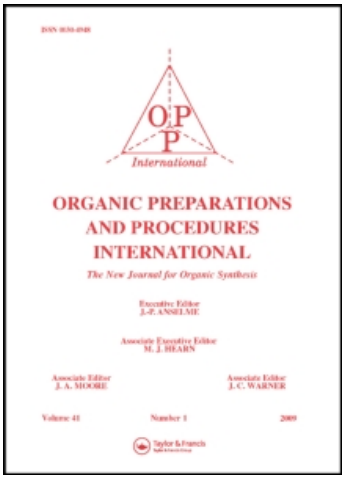

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Newton, Linda S. , Chan, Samantha , Sitter, Barbara J. , Brenek, Steven J. , Raggon, Jeffery W. and Braish, Tamim F.(1995) 'A PRACTICAL SYNTHESIS OF 4-BROMO-2-CYANO-3-METHYL-2-BUTENENITRILE', Organic Preparations and Procedures International, 27: 6, 695 — 697
To link to this Article: DOI: 10.1080/00304949509458535
URL: http://dx.doi.org/10.1080/00304949509458535

A PRACTICAL SYNTHESIS OF 4-BROMO-2-CYANO-3-METHYL-2-BUTENENITRILE

Submitted b (03/28/95)

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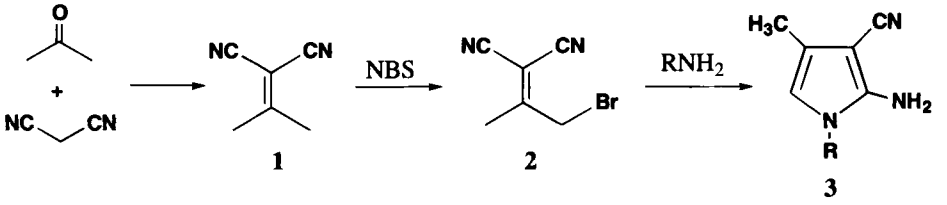
We required large quantities of 4-bromo-2-cyano-3-methyl-2-butenenitrile (**2**),[1] a useful intermediate in the synthesis of aminopyrroles **3**.[1,2] The known procedure involves a Knoevenagel

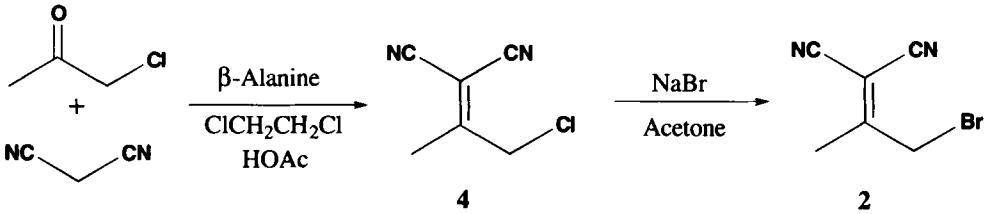


1 2 3

condensation[3] of malononitrile with acetone to yield **2** which was brominated to give **1**.[2]

While the first step works well on large scale, the bromination step provides, in addition to the desired product **2**, some of the dibrominated material and unreacted starting material **1**. The product ratio from the bromination reaction varied with each experiment and a difficult distillation at high vacuum was necessary to purify **2**.

In order to avoid these difficulties, we examined an alternative approach to **2** *via* the condensation of malononitrile with chloroacetone to give **4** followed by a chlorine-bromine exchange.[4] This route proved to be far more efficient and reproducible. Thus chloroacetone was heated with malononitrile in toluene or 1,2-dichloroethane, with five equivalents of acetic acid and catalytic amounts of β-alanine (0.1 eq.). Whereas the solvent was not critical for this reaction, the temperature was; there was little or no reaction at room temperature and tars formed at temperatures exceeding 60°. Ideally, 45° was the temperature at which the best yield was obtained with minimum tar formation. The combination of acetic acid/β-alanine[5] was far superior to the acetic acid/piperidinium acetate[6] or acetic acid/ammonium acetate[7] combinations typically used in the Knoevenagel condensation.



4 2

The chloro compound **4** was isolated cleanly in 50-55% yield by washing the reaction mixture with water several times to remove unreacted malononitrile. Intermediate **4** failed to react

with amines to afford pyrroles. Consequently, treatment of **4** with 5 equivalents of sodium bromide in acetone provided **2** in 97% yield of sufficient purity to be used without distillation, for the preparation of aminopyrroles **3**.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Brücker 300 MHz spectrometer in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectral data were obtained on a Hewlett-Packard 5890 GC (HP-1 12 m capillary column) in tandem with an HP Model 5971A Mass Selective Detector. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory (56-19 37th Avenue, Woodside, NY 11377). All reagents were purchased from Aldrich Chemical Company and used as received.

WARNING: *Chloroacetone is a severe lachrymator and should be handled in a well ventilated hood.*

4-Chloro-2-cyano-3-methyl-2-butenenitrile (**4**) To a solution of malononitrile (66.0 g, 1.0 mol) in 3.5 L of toluene was added the chloroacetone (111 g, 1.2 mol), acetic acid (40 mL, 0.70 mol), and β-alanine (9.0 g, 0.1 mol). The reaction was stirred at 45-50° for 8 hrs.[8] The mixture was cooled to 0° and decanted from a tar-like by-product and the organic layer was washed with water (4 x 500 mL) and dried over $MgSO_4$. Evaporation of the solvent provided 66.2 g (47%) of product **4** . This material was used in the next step without purification. If desired, purification may be accomplished by vacuum distillation, bp. 92-93°/1mm Hg. ^1H NMR: δ 4.22 (s, 2H), 2.44 (s, 3H). FTIR (neat): 2237, 1608, 1429, 1378, 732 cm^{-1}. GCMS m/e: 142 (M^++2), 140 (M^+), 105, 78.

Anal. Calcd for $C_6H_5ClN_2$: C, 51.27; H, 3.58; N, 19.93. Found: C, 51.21; H, 3.62; N, 19.92

4-Bromo-2-cyano-3-methyl-2-butenenitrile (**2**) To a solution of intermediate **4** (116.0 g, 0.83 mol) in 500 mL of acetone, was added anhydrous sodium bromide (255.0 g, 2.50 mol). The mixture was stirred vigorously using an overhead stirrer, at room temperature for 16 hrs. The resulting slurry was filtered, the solids washed with 50 mL of acetone and the filtrate diluted with 350 mL of CH_2Cl_2. The filtrate was then washed with 350 ml of water, dried over $MgSO_4$, and concentrated to give 90 g (97%) of **1** as light brown oil. This intermediate was stored at 0° due to its limited shelf-life at room temperature. ^1H NMR: δ 4.35 (s, 2H), 2.42 (s, 3H). FTIR (neat): 2236, 1603, 1447, 1432, 1377, 608 cm^{-1}. Exact mass Calcd. for $C_6H_5BrN_2$: 183.9636. Found: 183.9641.

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8. The progress of the reaction was followed by capillary GC (Hewlett-Packard): Capillary column 10m X 0.35 mm Carbowax HP-20M; Temp. 1 = 50°, time 1 = 2 min. Rate of heating = 15°/min, Helium flow = 6 ml/min. Temp. 2 = 210°, Time 2 = 3 min.

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NEW METHOD FOR THE PREPARATION OF GUANYLTHIOUREAS

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Guanylthiourea (**3a**), often referred to as *gutimine*, is a frequent starting material in preparation of many thiazoles and has been prepared by the reaction of saturated aqueous hydrogen sulfide with N-cyanoguanidine (dicyandiamide, **1a**) at 60-80°.[1] Gutimine also results from the acid hydrolysis of 4,6-diamino-2-thio-1,3,5-thiadiazine[2] and in the dehydrosulfurization of alkyl dithiocarbamic acids as by-product.[3] It was also prepared and used as intermediate for the synthesis of triazines by reacting dicyandiamide with hydrogen sulfide in N-alkylpyrrolidone as solvent, using amines, ammonia, and/or sulfur as catalyst.[4] All of these methods are characterized by *e. g.* elevated temperatures, non aqueous solvents, long reaction times, and reagents which are dangerous and/or bad-smelling such as hydrogen sulfide or carbon disulfide.

We now report that guanylthiourea (**3a**) can be produced by reacting dicyandiamide (**1a**) and sodium thiosulfate in acidic medium followed by neutralization with a base. It is rather surprising that sodium thiosulfate can be used as source of hydrogen sulfide in the production of gutimine, because it is well known that free thiosulfuric acid readily decomposes by adding *sulfur, sulfur dioxide*, and *water*, not *hydrogen sulfide* and *sulfuric acid.*