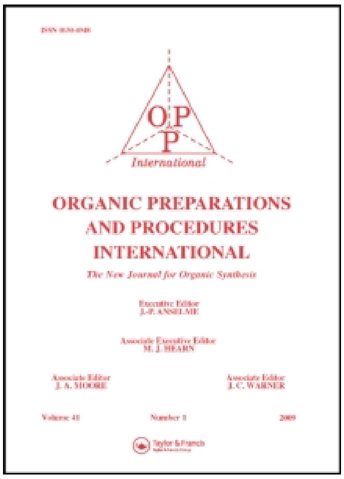

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF GUANYLUREIDO ACIDS

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To cite this Article Nakanishi, Susumu(1974) 'AN IMPROVED SYNTHESIS OF GUANYLUREIDO ACIDS', Organic Preparations and Procedures International, 6: 5, 235 — 238

To link to this Article: DOI: 10.1080/00304947409355111

URL: http://dx.doi.org/10.1080/00304947409355111

ORGANIC PREPARATIONS AND PROCEDURES INT. 6(5), 235-238 (1974)

AN IMPROVED SYNTHESIS OF GUANYLUREIDO ACIDS

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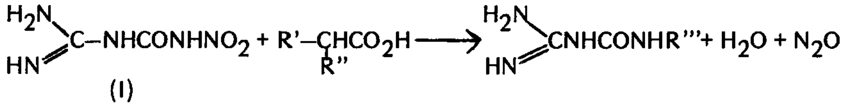
The reaction of N-amidino-N'-nitrourea with amino acids has long been known as a method for preparing α-aminoureido acids.[1] This procedure, however, affords variable and frequently low yields of the desired acids. We report herein an improved method which provides dependable, high yields of guanylureido acids.

The reaction of amino acids and N-amidino-N'-nitrourea proceeds as outlined in equation 1. Because of the poor solubility of both amino acids and N-amidino-N'-nitrourea (I) in organic solvents, the reaction is best carried out in water. However, it has been established[2] that water attacks the N-amidino-N'-nitrourea in a competing reaction [cf., equation 2], thus liberating guanidine (VIII) and generating a strongly alkaline medium. Furthermore, the rate of decomposition of nitroureas in water is increased by alkaline catalysts such as amines.[2] Moreover, the substituted ureas are transformed in aqueous solution into either a primary amine and isocyanic acid or an isocyanate and ammonia.[3] Although Frankel et al.[1] reported a 69% yield of V, in our hands, yields of V by condensation of I with glycine in water varied between 40 to 54%.

(1)



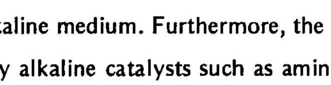
II $R' = NH_2$, $R'' = H$

III $R' = C_6H_5$, $R'' = NHCOCH_2NH_2$

IV $R' = (CH_3)_2CHCH_2$, $R'' = NH_2$

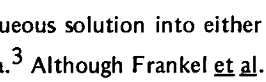
V $R''' = CH_2CO_2H$

VI



$R''' = -CH_2CONH-\underset{\displaystyle C_6H_5}{\underset{|}{C}}H-CO_2H$

VII



$R''' = -\underset{\displaystyle CH_2CH(CH_3)_2}{\underset{|}{C}}H-CO_2H$

(2)

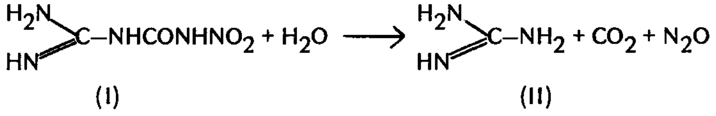
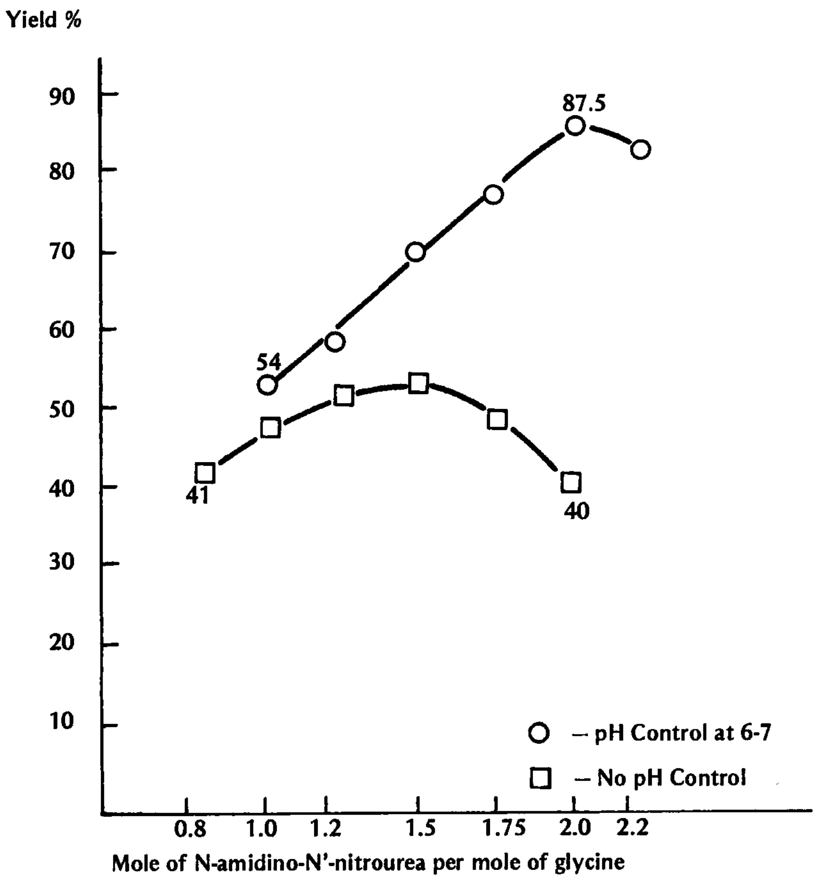


CHART I

EFFECT OF pH ON YIELD OF GUANYLUREIDOACETIC ACID



Notes: 1) All experiments were carried out in H_2O [200 ml H_2O per 0.1 mole of glycine]. 2) The reaction mixture was refluxed for 2 hrs. at 95-97°. 3) Isolation was carried out at pH 6.8 (near its isoelectric point).

By maintaining the reaction mixture at pH 6-7 and adjusting to pH 6.8 (isoelectric point) prior to the isolation, we obtained amidinoureidoacetic acid (V) in 87.5% yield. The effect of pH control is dramatically illustrated in Chart I where the yield of guanylureidoacetic acid (V) obtained at pH 6 to 7 is more than two-fold higher than that observed without pH control. In most cases, the amino acid is the limiting reagent and thus use of an excess of N-amidino-N'-nitrourea to improve yields is obviously advantageous. Application of our improved procedure to the D(—)-glycyl-2-phenylglycine (III)[4] gave the corresponding guanylureido acid (VI) in 70% yield. Similarly, L-leucine with N-amidino-N'-nitrourea gave (VII) in 71% yield, in contrast to the reported[1] yield of 12%.

EXPERIMENTAL

Guanylureidoacetic acid (V).[1]— A suspension of 29.4 g (0.2 mole) of N-amidino-N'-nitrourea (I)[5], and 7.5 g (0.1 mole) of glycine (II) in 200 ml of water was adjusted from initial pH of 3.8 to pH 6.0 with 10% aqueous NaOH. The mixture was then refluxed for 2 hrs at 95-97°, while the pH of the solution was maintained between 6 and 7 by periodic addition of 10% HCl. The reaction mixture was cooled to 10° and the pH was readjusted to 6.8. The resulting solid product was collected by filtration, washed with 500 ml of water until the ninhydrin test was negative, and dried *in vacuo* to give 14 g (87.5%) of V, mp 203-205°, lit.[1] mp 205°. Neutralization equivalent: Calcd. 160.1; found 161. The previously assigned structure was confirmed by U.V., I.R., N.M.R. in addition to a correct elemental analysis.

D(—)-N-guanylureidoacetyl-α-aminophenylacetic (VI). — The pH of a mixture of 1 g (5 mmoles) of D(—)-glycyl-2-phenylgycine (III)[4] and 1.47 g (10 mmoles) of N-amidino-N'-nitrourea (I) in 20 ml of water was adjusted from pH 3.8 to pH 6.0. The mixture was then heated to reflux at 95-98°. During the 2 hrs reflux, the pH of the reaction was kept between pH 6 and 7 by addition of 1% aqueous HCl. The reaction mixture was then cooled to 10° and the pH was adjusted to 8.5 by addition of 2% aqueous NaOH to neutralize hydrochloride. After stirring for 2 minutes, the pH was readjusted to the isoelectric point of 6.8 by addition of 1% aqueous HCl. Filtration, followed by a water wash and air-drying overnight at room temperature gave 980 mg (70%) of VI, mp 221-222° (dec.); Karl-Fischer water 1.42%.

Anal: Calcd. for $C_{12}H_{15}O_4N_5$ 1.42% H_2O: C, 48.41; H, 5.24;
N, 23.53. Found: C, 48.22; H, 5.13; N, 22.74

N-guanylureido-α-isobutylacetic acid (VII)[1]. – The pH of a suspension of 13.1 g (0.1 mole) of L-leucine (IV), 29.4 g (0.2 mole) of N-amidino-N'-nitrourea (I), and 200 ml of water was adjusted from 3.7 to 6.5. The mixture was heated slowly to reflux at 95-97°. During the 2 hrs reflux, pH of the reaction was kept between pH 6 to 7 by addition of 10% HCl. The reaction mixture was cooled to 10° and pH was adjusted to 8 with 10% aqueous NaOH, then to pH 6.8 (isoelectric point) with 10% HCl. Filtration, followed by a water wash and air-drying gave 15.4 g (71.2%) of VII, mp 204-205°, lit.[1] mp 200-205°; Karl-Fischer water 0.55%; Neutralization equivalent: Calcd. 217.5; found 218. The previously assigned structure was confirmed by U.V., I.R., N.M.R. in addition to a correct elemental analysis.

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(Received August 13, 1974; in revised form October 24, 1974)