An Improved Synthesis of [1*H*]-Isoindolin-1-one-3-carboxylic Acid

John A. Lowe, III* and Frank E. Ewing

Central Research Division, Pfizer, Inc.,
Groton, CT 06340

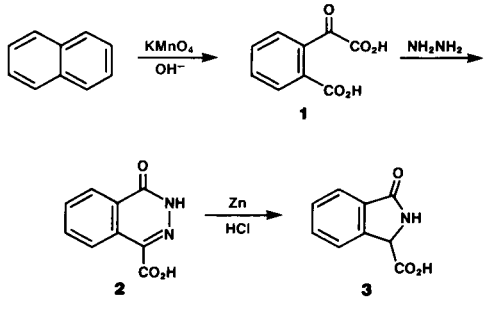
Received March 2, 1987

Preparation of the title compound in one operation from commercially available phthalaldehydic acid in 34% yield is described.

J. Heterocyclic Chem., **24**, 877 (1987).

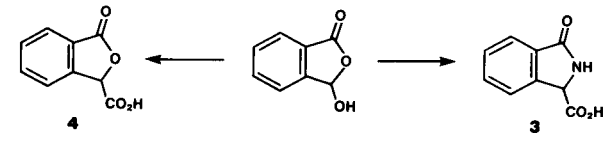
[1*H*]-Isoindolin-1-one-3-carboxylic acid (**3**) is potentially useful as a surrogate for the amino acids proline or phenylglycine in the design of biologically active molecules. The literature [1] preparation of the compound, however, is sufficiently difficult to deter attempts to exploit this potential. It involves preparation of phthalonic acid, **1** (Scheme I), from naphthalene in 53-63% yield, followed by conversion to intermediate **2** in 72% yield, and finally reduction with zinc in hydrochloric acid to afford the desired product **3** in 25% yield. It is at best, then, a tedious procedure giving only 9-11% overall yield. In order to facilitate the synthesis of **3**, we have developed a simplified route to this useful molecule.

Scheme I



When a Strecker synthesis was attempted on the commercially available phthalaldehydic acid [2] under the usual conditions, the lactone **4** was found to be the major product (Scheme II). In order to incorporate the lactam nitrogen, the usual procedure was modified by first treating the aldehyde [2] with ammonia in methanol, followed by addition of cyanide and subsequent hydrolysis. The modified procedure resulted in a 34% yield of the desired lactam **3** following one recrystallization. Compound **3** displayed physical properties in complete agreement with those described in the literature. Though the yield is modest, it is reproducible over several experimental runs, and the ready availability of the starting material and ease of operation allow facile access to this useful compound.

Scheme II



EXPERIMENTAL

[1*H*]-Isoindolin-1-one-3-carboxylic Acid (**3**).

Ammonia gas was bubbled into a cooled (10-15°) solution of 10 g (0.0666 moles) of phthalaldehydic acid in 100 ml of methanol for 10 minutes. The solution was then let stir at room temperature for 1 hour. To the stirred solution was then added a solution of 3.26 g (0.0666 mole) of sodium cyanide in 100 ml of water over a 15 minute period, producing a slight exotherm to a temperature of 30°. The resulting solution was stirred at room temperature for 1 hour, and most of the methanol evaporated *in vacuo*. To the resulting yellow solution was added dropwise 80 ml of 6*N* hydrochloric acid over 10 minutes, producing a transient precipitate followed by redissolution. The solution was then heated at 100° for 1.5 hours, producing a thick yellow precipitate. The reaction mixture was cooled to room temperature, the yellow solid filtered and washed with water and acetone. The resulting solid was crystallized from water to give 4.14 g (34%) of pale yellow crystals, mp 153-154° (lit [1], mp 152°); ir (potassium bromide): 1708 cm^{-1} (C=O) and 1634 cm^{-1} (CO_2H) (in agreement with literature values [3]); ^1H nmr (dimethyl sulfoxide): δ 5.25 (s, CH, 1H), 7.4-8.0 (m, aromatic and NH, 5H), 8.84 (s, CO_2H, 1H); ms: 177 (M^+, 6), 132 (M-44, 100).

REFERENCES AND NOTES

[1] A. Darapsky and P. Heinrichs, *J. Prakt. Chem.*, **146**, 307 (1936).

[2] Purchased from Aldrich Chemical Company.

[3] T. Kametani, H. Suguhara and K. Kanno, *Chem. Pharm. Bull.*, **15**, 1916 (1967).