Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Application of the Curtius Rearrangement in a Convenient Preparation of 3-Aminopyrazinecarboxylic Acid, Methyl Ester

Jiong J. Chen [a], Jack M. Hinkley [a], Dean S. Wise [a] & Leroy B. Townsend [a]

[a] Department of Chemistry, College of Literature, Science, & The Arts; Department of Medicinal Chemistry, College of Pharmacy, The University of Michigan, Ann Arbor, MI, 48109

Version of record first published: 21 Aug 2006

To cite this article: Jiong J. Chen, Jack M. Hinkley, Dean S. Wise & Leroy B. Townsend (1996): Application of the Curtius Rearrangement in a Convenient Preparation of 3-Aminopyrazinecarboxylic Acid, Methyl Ester, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:3, 617-622

To link to this article: http://dx.doi.org/10.1080/00397919608003656

SYNTHETIC COMMUNICATIONS, 26(3), 617-622 (1996)

APPLICATION OF THE CURTIUS REARRANGEMENT IN A CONVENIENT PREPARATION OF 3-AMINO-PYRAZINECARBOXYLIC ACID, METHYL ESTER

Jiong J. Chen, Jack M. Hinkley, Dean S. Wise, Leroy B. Townsend*

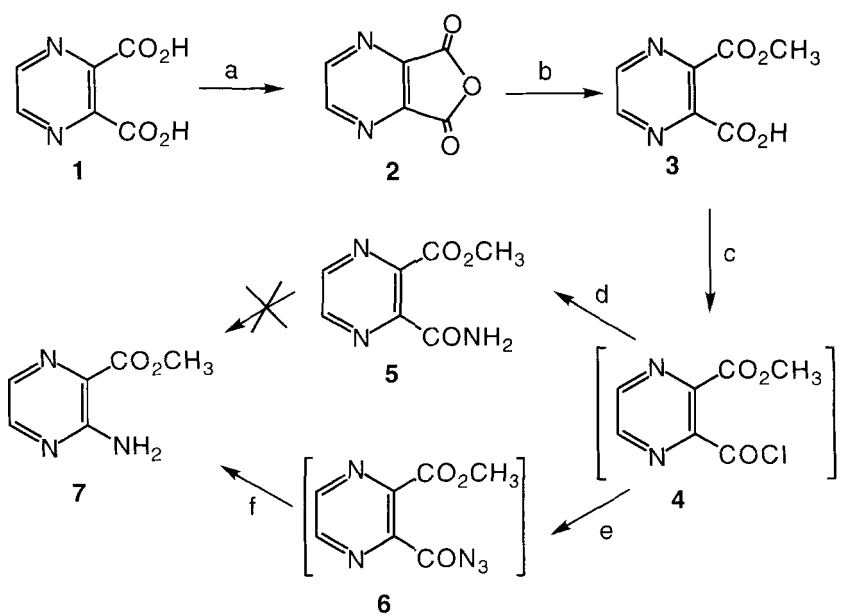
Department of Chemistry, College of Literature, Science, & The Arts; Department of Medicinal Chemistry, College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109

ABSTRACT: An efficient and convenient synthesis of 3-aminopyrazinecarboxylic acid, methyl ester (**7**) has been achieved through the use of a Curtius rearrangement.

3-Aminopyrazinecarboxylic acid, methyl ester (**7**) is a useful intermediate for the preparation of polysubstituted pyrazines and pteridines. However, compound **7** was not readily available in the quantities we required for one of our research projects. A search of the literature[1] revealed that the most efficient preparation of **7** is by a hydrolytic cleavage of lumazine[2,3] to furnish 3-aminopyrazinecarboxylic acid followed by an esterification[4]. However, these conditions, high temperature and concentrated sulfuric acid, only provide the product in fair yield. More recently, Buckland[5] has shown that the treatment of furo[3,4-*b*]pyrazine-5,7-dione (**2**) (2,3-pyrazinedicarboxylic acid anhydride) with anhydrous ammonia gives the ammonium salt of 3-(aminocarbonyl)pyrazinecarboxylic acid in a high yield. This compound then underwent a Hoffmann rearrangement to give 3-aminopyrazinecarboxylic acid. This prompted us to initiate studies designed to produce **7** in a high yield.

* To whom correspondence should be addressed.

Following the procedure of Buckland[5], the reaction of 2,3-pyrazinedicarboxylic acid (**1**) with acetic anhydride gave furo[3,4-*b*]pyrazine-5,7-dione (**2**). The reaction of **3** with methanol gave a quantitative yield of 2,3-pyrazinedicarboxylic acid, monomethyl ester (**3**)[6]. Treatment of **3** with thionyl chloride presumably gave the acid chloride **4**, which was not isolated, but was reacted with hexamethyldisilazane followed by hydrolysis to afford 3-(aminocarbonyl)pyrazinecarboxylic acid, methyl ester (**5**). Attempts to prepare **7** by a Hoffmann rearrangement of **5** under a variety of reaction conditions[7] met with little success. On the other hand, the reaction of **4** with sodium azide gave the intermediate acyl azide **6**, which without isolation smoothly underwent a Curtius rearrangement[8] to give **7** in 86% yield (80% overall yield from **1**). This would appear to be a useful and general method for the preparation of other derivatives of 3-aminopyrazinecarboxylic acid.



(a) Ac_2O/Δ; (b) CH_3OH, RT; (c) $SOCl_2/CHCl_3/\Delta$; (d) $HN(SiMe_3)_2$, 0°C /H_2O, Δ; (e) NaN_3/Acetone/H_2O, 0°C; (f) PhH/Δ.

Experimental:

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker AM 300 MHz or 200 MHz spectrometer, and the chemical shift values are reported in parts per million on the δ scale. Thin layer chromatography (TLC) was performed on Analtech silica gel-GF plates and spots were visualized by UV. "Concentrated" means that solvents were evaporated with a rotary evaporator under water aspirator reduced pressure at 35 °C. "Dried" means that a solid was dried over P_2O_5 under water aspirator reduced pressure at 35 °C. Solvents were used without distillation. 2,3-Pyrazinedicarboxylic acid (**1**) was obtained from TCI and Aldrich Chemical Company. Other commercially available reagents were used as received. Microanalysis was performed by the CHN laboratory , Department of Chemistry, The University of Michigan.

Furo[3,4-*b*]pyrazine-5,7-dione (2,3-pyrazinedicarboxylic acid anhydride) (2): A suspension of 2,3-pyrazinedicarboxylic acid[9] (**1**) (500 g, 3.0 mol) in acetic anhydride (1.3 L), protected from moisture with a calcium sulfate drying tube, was heated at reflux temperature until a brown solution had formed. Heating was continued for an additional 10 min, the mixture was then cooled to 0 °C at which time a solid crystallized. The white crystalline solid[10] was collected by filtration, washed with ether (300 mL), then dried to afford 415 g (93%) of **2**. Mp: 223-224 °C (dec. > 200 °C) (lit.[5] 221-222 °C); ^{1}H NMR ($CDCl_3$): δ 9.18 (s).

2,3-Pyrazinedicarboxylic acid, monomethyl ester (3): Compound **2** (410 g, 2.7 mol) was added to methanol (2.5 L) in 4 portions over a period of 1 h. The yellow solution was stirred at room temperature for 12 h, and then concentrated to dryness to afford 497 g (100%) of **3** as a white solid. Mp: 114-116 °C (lit.[6] 115-116 °C); ^{1}H NMR (DMSO-d_6/D_2O): δ 3.88 (s, 3H), 8.87 (m, 2H).

3-(Chlorocarbonyl)pyrazinecarboxylic acid, methyl ester (4): Thionyl chloride (167 mL, 272 g, 2.28 mol) was added over a period of 45 min at room temperature to a suspension of **3** (150.0 g, 0.82 mol) in chloroform (1.5 L) which contained DMF (2 mL). After the mixture was heated at reflux temperature for 3 h, more thionyl chloride (10 mL, 16.0 g, 0.14 mol) was added and the mixture was heated at reflux temperature for an additional 60 min. The resulting black solution was concentrated and the remaining trace amount of thionyl chloride was removed by distillation as an azeotrope with benzene to give 164 g of **4** as a brown oil which was used directly in the next step without further purification.

3-Aminopyrazinecarboxylic acid, methyl ester (7): A solution of sodium azide (130 g, 2.0 mol) in water (430 mL) was added over a period of 20 min to a solution of **4** (151 g, 0.75 mol) in acetone (3.3 L) at 0 °C. The resulting suspension was stirred at 0 °C for 18 h. Water (350 mL) was added to dissolve the precipitate, and the resulting solution was then extracted with benzene (850 mL X 3). The combined benzene extracts were slowly[10] heated to reflux temperature and then heated at reflux for 24 h. The solution was cooled and then concentrated to dryness. The resulting solid residue was recrystallized from aqueous methanol to give 99.0 g (86%, based on **3**) of **7** as a yellow solid. Mp: 174-174.5 °C (lit.[4] 172-173 °C); R_f = 0.5 (EtOAc : hexane (v/v) = 1 : 1); ^{1}H-NMR (DMSO-d_6): δ 3.83 (s, 3H), 7.33 (b, 2H, exchangeable with D_2O), 7.89 (d, 1H), 8.25 (d, 1H).

3-(Aminocarbonyl)pyrazinecarboxylic acid, methyl ester (5): Hexamethyldisilazane (19 g, 25 mL, 0.12 mol) was slowly added to a solution of **4** (10.06 g, 0.05 mol) in chloroform (80 mL) at 0 °C. The resulting mixture was heated at reflux temperature for 90 min, and then concentrated to dryness. Water (70 mL) was added to the residue, and this aqueous solution was heated at reflux

temperature for 30 min to form a precipitate. After cooling to 0 °C, the precipitate was collected by filtration and dried to afford 6.80 g (75%) of **5** as a white solid. Mp: 175-176 °C. R_f = 0.2 (EtOAc : hexane (v/v) = 1 : 2); ^{1}H-NMR (DMSO-d_6): δ 3.85 (s, 3H), 7.95 (s, 1H, exchangeable with D_2O), 8.35 (s, 1H, exchangeable with D_2O), 8.85 (m, 2H); Elemental anal. for $C_7H_7N_3O_3$, calcd.: C, 46.41, H, 3.89, N, 23.20; found: C, 46.22, H, 3.99, N, 23.27.

Acknowledgment: This work was financially supported by Grant RO1-CA56842, awarded by the National Cancer Institute, National Institutes of Health.

References:

1. Barlin, G. B., "The Pyrazines, The Chemistry of Heterocyclic Compounds - A Series of Monographs," John Wiley & Sons, New York, **1982**, pp. 247-377.
2. Bogert, M. T. and Davidson, D., *J. Am. Chem. Soc.*, **1933**, *55,* 1667-1668.
3. Weijlard, J., Tishler, M. and Erickson, A. E., *J. Am. Chem. Soc.*, **1945**, *67,* 802-806.
4. Ellingson, R. C., Henry, R. C. and McDonald, F. G., *J. Am. Chem. Soc.*, **1945**, *67,* 1711-1713.
5. Buckland, P. R., *J. Heterocycl. Chem.*, **1980**, *17,* 397-398.
6. Solomons, I. A. and Spoerri, P., *J. Am. Chem. Soc.*, **1953**, *75,* 679-681.
7. (a) Magnien, E. and Baltzly R., *J. Org. Chem.*, **1958**, *23,* 2029-2032. (b) Baumgarten, H. E., Smith, H. L. and Staklis, A., *J. Org. Chem.*, **1975**, *40,* 3554-3561.
8. Smith, P. A. S., "Organic Reactions III," John Wiley & Sons, New York, **1947**, pp. 337-450.
9. Jones, R. G., McLaughlin, K. C., "Organic Synthesis, Collective Vol IV," John Wiley & Sons, New York, **1963**, pp. 824-827.

10. Moisture will hydrolyze this compound to furnish 2,3-pyrazinedicarboxylic acid.

11. Organic azides may be explosive, thus, caution should be exercised. However, we have not encountered any problems up to a 500 g scale of this reaction in our lab.

(Received in the USA 06 June 1995)