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First Example of a 1-Aminoquinazoline-2,4-dione

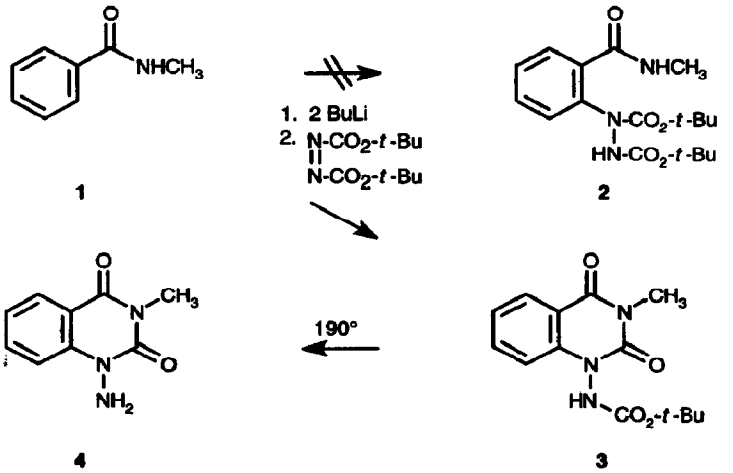
James P. Demers

Department of Medicinal Chemistry
The R. W. Johnson Pharmaceutical Research Institute
P.O. Box 300, Raritan, NJ 08869-0602

Abstract: Aromatic hydrazination of ortho-lithiated N-methylbenzamide occurs with cyclization to provide a protected derivative of the novel 1-aminoquinazoline-2,4-dione.

The hydrazination of aryllithiums and arylmagnesium halides with di-*t*-butyl azodicarboxylate, an extension of Carpino's original observations,[1] was developed in these laboratories as a convenient route to certain arylhydrazines.[2] The application of this chemistry to ortho-lithiated derivatives of benzoic acids was subsequently investigated as a short and convenient synthesis of indazolin-3-ones.[3]

In the course of these investigations, N-methylbenzamide **1** was deprotonated and *ortho*-lithiated with n-butyllithium,[4,5] and di-*t*-butyl azodicarboxylate was added to the resulting dilithium species. The major product after an aqueous workup was not the expected *ortho*-hydrazino derivative **2**: examination of the NMR spectrum showed the presence of only a single *t*-butoxycarbonyl group, along with four aromatic protons, the N-methyl singlet, and one exchangeable proton. The infrared spectrum exhibited three strong carbonyl stretches. Structure **3** was assigned to this material, based on the spectral data and on elemental analysis. A search of the chemical literature surprisingly turned up no examples of 1-aminoquinazolinediones.[6]



Removal of the protecting group from **3** with acid resulted in decomposition, but thermolysis *in vacuo* [7] provided the parent 1-aminoquinazolinedione **4** in 72% yield. All spectral data for **4** were in accord with the assigned structure, the NH_2 protons giving rise to an exchangeable 2H singlet in the ^1H NMR spectrum. A doublet, due to NH_2 symmetric and asymmetric stretching vibrations, was expected in the infrared spectrum, but only a single sharp N–H stretch at 3339 cm^{-1} was observed. N-aminophthalimide likewise exhibits only a single sharp absorption.

Attempts to prepare salts with mineral acids led to decomposition of **4**, but the material is otherwise stable to ambient conditions. Since **4** is a cyclic semicarbazide, the formation of semicarbazone derivatives was attempted, and crystalline derivatives of aromatic aldehydes were readily obtained in warm acetic acid. It is hoped that the ready availability of **4** will also make accessible a variety of novel fused heterocycles.

The formation of **3** was unexpected, due to the generally unreactive nature of carbamates and due to the fact that the cyclization involves attack of one anionic species on another. There is precedent for the formation of cyclic ureas by addition of amide anions to the carbonyl of a *t*-butylcarbamate,[8] so the cyclic nature of the transition state apparently overcomes these barriers. Coordination of the carbamate carbonyl to lithium may also play a role. The nucleophilicity of the N-methyl amide anion is also a controlling factor, since exposure of N-phenyl benzamide to the same reaction conditions cleanly affords the expected product corresponding to **2** with no evidence of cyclization, at least at 0°. This can reasonably be ascribed to reduced electron density at nitrogen in the N-phenylbenzamide anion, relative to the N-methyl analogue.

EXPERIMENTAL PROCEDURES

1-(t-Butoxycarbonylamino)-3-methyl-2,4(1H,3H)-quinazolinedione (3): A solution of N-methylbenzamide (3.38 g, 25 mmol) in anhydrous tetrahydrofuran (100 ml) was cooled under a nitrogen atmosphere to -70°. A solution of *n*-butyllithium (2.5 M in hexane, 21 ml, 52 mmol) was added dropwise with stirring, and the resulting solution was allowed to warm to 0°. The solution was stirred at 0° for 40 min in order to effect dimetallation, resulting in the formation of a precipitate. The suspension was cooled to -70° and a solution of di-*t*-butyl azodicarboxylate (5.76 g, 25 mmol) in tetrahydrofuran (25 ml) was added quickly with stirring. A transient dark brown color formed, and then faded as an exothermic reaction ensued. The temperature rose to about -30°; the cooling bath was removed and the mixture was allowed to warm further to 0°. Aqueous 1.0 N hydrochloric acid (50 ml) was added, and the mixture extracted with hexane (2 x 50 ml). The hexane extracts were dried ($MgSO_4$), filtered, and evaporated, and the residue allowed to crystallize overnight from warm carbon tetrachloride (50 ml), providing 3.2 g (44%) of **3** as a white powder, mp 180-182° dec. An analytical sample was crystallized from CCl_4-$CHCl_3$, mp 182-183° dec.

Analysis calc./found for $C_{14}H_{17}N_3O_4$: H 5.88/6.03, C 57.72/57.25, N 14.42/14.73
IR (KBr) 3279, 1750, 1705, 1662, 1608 cm^{-1}
^1H NMR ($CDCl_3$) δ 8.18 (d, J=7.9 Hz, 1H), 7.67 (t, J=7.8 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H), 7.28 (t, J=7.9 Hz, 1H), 6.86 (br s, 1H, D_2O exch.), 3.49 (s, 3H), 1.53 (br s, 9H).

1-Amino-3-methyl-2,4(1H,3H)-quinazolinedione (4): A sample of **3** (2.0 g, 6.87 mmol) was placed in a small flask on a vacuum line, and heated to its melting point *in vacuo*. When gas evolution ceased, the sample was cooled and the residue recrystallized from isopropanol (75 ml) to provide 0.95 g (72%) of **4** as a white powder, mp 178-179°.

Analysis calc./found for $C_9H_9N_3O_2$: H 4.74/4.78, C 56.54/56.44, N 21.98/21.79
IR (KBr) 3339, 1699, 1657, 1633, 1620, 1606 cm^{-1}
^1H NMR ($CDCl_3$) δ 8.15 (dd, J=1.5, 7.9 Hz, 1H), 7.87 (d, J=7.9 Hz, 1H), 7.69 (dt, J=1.5, 7.9 Hz, 1H), 7.24 (t, J=7.9 Hz, 1H), 4.65 (s, 2H, D_2O exch.), 3.50 (s, 3H).

REFERENCES AND NOTES

1. Carpino, L.; Terry, P.; Crowley, P. *J. Org. Chem.*, **1961**, *26*, 4336
2. Demers, J.; Klaubert, D. *Tetrahedron Lett.*, **1987** *28*, 4933
3. Demers, J. **1989** *U.S. Patent* 4,864,032
4. Gschwend, H.;Rodriguez, H. *Org. React.*, **1979** *26*, 1 and 54
5. Mao, C.-L.; Barnish, I. T.; Hauser, C. H.*J. Heterocyclic Chem.*, **1969** *6*, 475
6. A 1-amino uracil with a fused cyclohexane (*i.e.* a 5,6,7,8-tetrahydro derivative of **4**) has been described in two German patents: *Chem. Abstr. 79*:38704b and *78*:111360x
7. Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.*, **1985** *26*, 6141; and Wasserman, H. H.; Berger, G. D. *Tetrahedron*, **1983** *39*, 2459
8. Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.*, **1988** *29*, 5725

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