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2-AMINO-3-CYANO-4,5-DIMETHYLFURAN AS PRECURSORS TO BUTENOLIDES AND ARYLACETIC ACIDS

Hooshang Kooshkabadi, Walter F. Schmidt, Stephen J. Cutler, Fiesal M. El-Kabbani,
and C. DeWitt Blanton, Jr.*

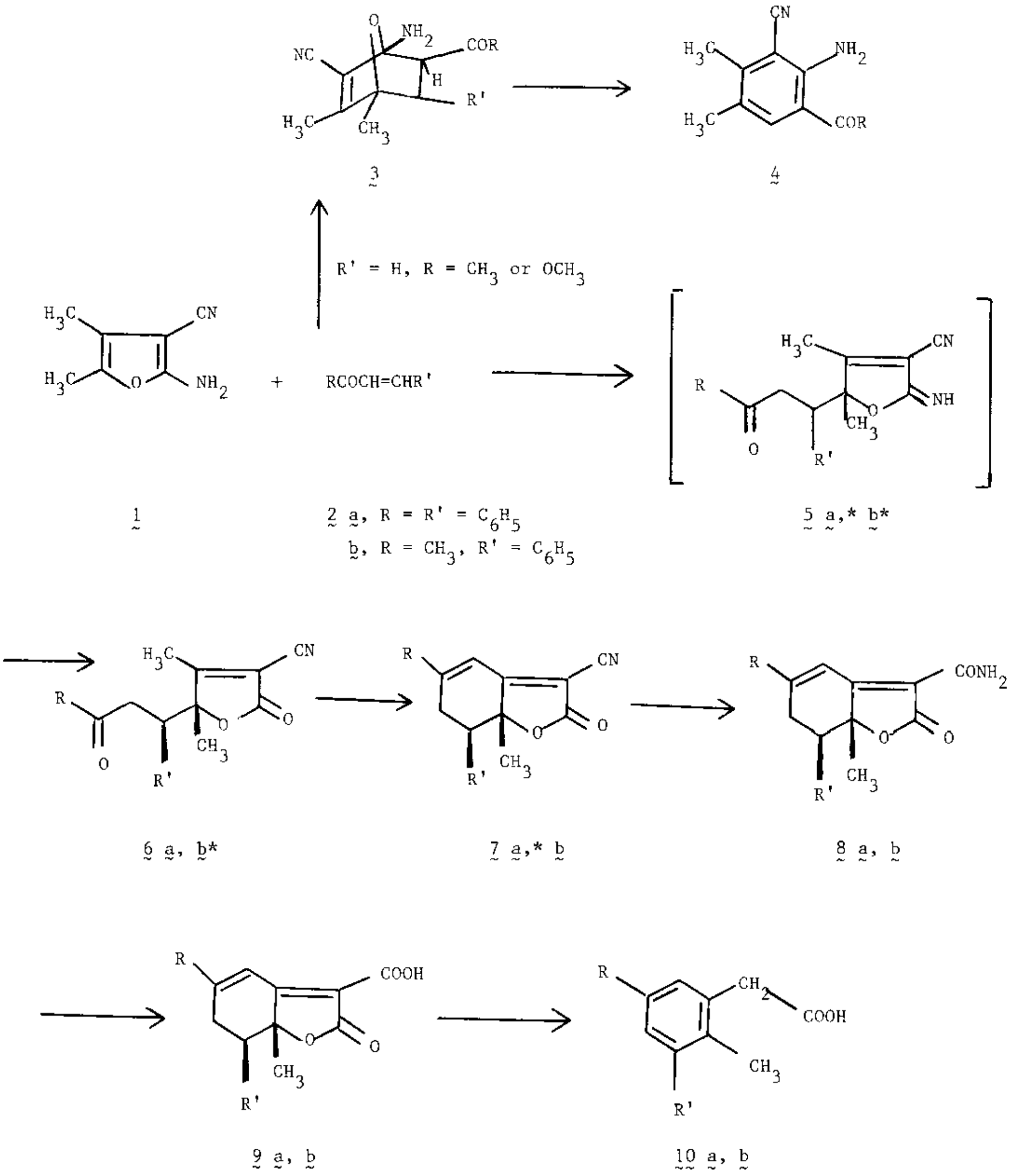
Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The
University of Georgia, Athens, Georgia 30602, USA

Abstract - A facile synthesis of butenolides and arylacetic acids via a Michael reaction of the title compound at C(5) is reported.

While investigating[1] the feasibility for utilizing various furan o-aminonitriles (e.g., 1, Scheme I) as dienes in Diels-Alder cycloaddition reactions with monoactivated dienophiles to synthesize highly substituted 2-aminobenzonitriles (4), we have now observed that certain dienophiles produce Michael product (5) rather than the expected cycloadduct (3). In contrast with the reaction between maleic anhydride and 4,5-disubstituted 2-amino-3-cyanofurans, which gave 2-aminobenzonitriles from Diels-Alder adducts,[2] a series of doubly activated dienophiles have been found to undergo predominately a Michael reaction at C-5.[3] The resulting products (e.g., 5) may be utilized to synthesize various $\Delta^{\alpha,\beta}$-butenolides and arylacetic acids. These compounds are of significant interest to researchers looking for synthetic routes to natural products containing the unsaturated lactone and possessing biological activity.[4] The procedures also represent new routes for the synthesis of potential antiinflammatory agents related to arylacetic and arylpropionic acids.[5]

Reaction of 2-amino-3-cyano-4,5-dimethylfuran (1)[2] with one equivalent of chalcone (2a) in refluxing dioxane for 16-18 h gave the Michael addition product 5, as a gum after removal of the solvent. The crude product was subjected to an acid-catalyzed hydrolysis with a mixture of acetic acid, water, and hydrochloric acid (1:1:0.15) at room temperature for 24 h to afford lactone (6a): mp 205-206°C (67.9%, benzene).[6] Treatment of 6a with polyphosphoric acid at 110-120°C for 3 h, followed by addition of ice-water, gave 8a: mp 204-205°C (55.3%, benzene).[8] The methyl hydrogens at C-4 are sufficiently acidic to allow the acid-mediated intramolecular aldol cyclization to the bicyclic γ-lactone (7a) with simultaneous hydrolysis of the cyano group. The amide 8a was hydrolyzed to the carboxylic acid 9a by heating in a mixture of acetic acid, sulfuric acid, and

SCHEME I



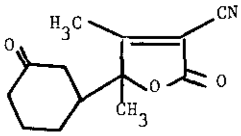
* Not isolated

water (2.5:1:1) at 175°C: mp 177-178°C (69.7%, benzene).[6] When amide **8a** was heated at 175°C in syrupy phosphoric acid, the arylacetic acid **10a** was obtained directly: mp 138-139°C (82.2%, benzene).[6]

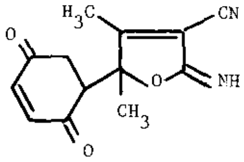
Reaction of trans-4-phenyl-3-buten-2-one (**2b**) with **1** followed a similar sequence. However, the acidic conditions observed to produce **6a** were found sufficient to yield directly bicyclic lactone **7b** without hydrolysis of the cyano group: mp 194-195°C (69.7%, 95% ethanol).[6]

Heating **7b** in a mixture of acetic acid and sulfuric acid (19:1) at 110°C for 15 h gave the amide **8b**: mp 249-251°C (68.5%, methanol).[6] On the other hand, heating **7b** in sulfuric acid, acetic acid, and water (1:1:1) at 110°C for 24 h gave the acid **9b**: mp 197-198°C (85.0%, ethanol).[6] When **7b** was heated with syrupy phosphoric acid at 175°C for 6 h, the arylacetic acid **10b** was obtained in near quantitative yields: mp 155-156°C (ethanol).[6]

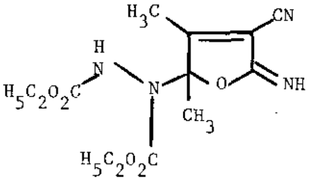
Presently, **1** has also been found to give Michael addition products with 2-cyclohexen-1-one (**6c**, mp 128-130°C; 57.1%, ethanol), 1,4-benzoquinone (**5d**, mp 186-187°C; 56.0%, acetone), diethyl azodicarboxylate (**5e**, mp 127-128°C; 74.2%, ethanol), and diethyl maleate (**5f**, mp 150-152°C; 78.9%, benzene).[6] In the last three examples, the imine intermediates (**5d**-**5f**) were easily isolated, and characterized, which were not the case for **5a**-**5c**. For the only example studied to date, the imine **5d** was conveniently converted by acid hydrolysis to the butenolide **6d**: mp 147-148°C.[6] Reaction of **1** with other dienophiles[7] and the chemistry of these systems is currently under study with particular emphasis on possible novel annulation products being derived from intermediates **6c**-**6f**.



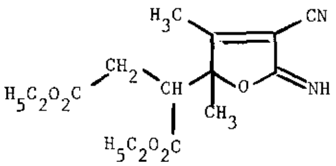
6c



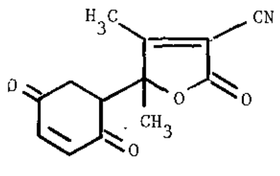
5d



5e



5f



6d

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2. K. Gewald, Chem. Ber., 1966, 99, 1002.
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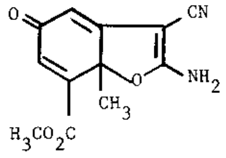
6. In these preliminary studies, no attempt has been made to optimize yields. The elemental analyses (C, H, and N, where appropriate, agree with calculated values within ±0.4%), ir, and ^{1}H-nmr spectra for all isolated products were in agreement with expected structures. Although a mixture of diastereomers is possible, it appears that one isomer predominates, at least with the bicyclic lactones. The stereochemistry of the diastereomers was tentatively assigned on the basis of nuclear Overhauser enhancement. NOE experiments (Bruker AM 500 showed enhancement (ca. 3%) of the phenyl signal in 6a and 8a upon irradiaton of the C-5 methyl moiety, while an NOE effect was not evident between the C-5 methyl and the adjacent hydrogen atom. Furthermore, coupling constants for 6a and 8a are consistent with the structural assignment. Spectral data for 6a: ir (KBr) 2225, 1765, 1685 cm^{-1}; ^{1}H-nmr (500 MHz, DMSO-d_6) δ 1.23 (s, 3H), 2.41 (s, 3H), 3.05 (dd, 1H, J = 17.7 Hz, J = 3.3 Hz), 3.61 (dd, 1H, J = 17.7 Hz, J = 10.3 Hz), 3.86 (dd, 1H, J = 10.3 Hz, J = 3.3 Hz), 7.20–7.85 (m, 10H, ArH). Spectral data for 8a: ir (KBr) 3420, 1735, 1670, 1625 cm^{-1}; ^{1}H-nmr (500 MHz, DMSO-d_6) δ 1.30 (s, 3H), 3.16 (dd, 1H, J = 17.18, J = 3.4), 3.47 (dd, 1H, J = 17.18, J = 11.47), 3.53 (dd, 1H, J = 11.47, J = 3.4), 7.05 - 7.85 (m, 11H).
7. A report[8] has recently appeared describing the reaction of 1 with dimethyl acetylenedicarboxylate in acetic acid to yield directly an annulated product:



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