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DIELS-ALDER REACTIONS OF A STYRENE-ISOCYANATE: UNEXPECTED FORMATION OF A PYRIDINONE AND URACIL

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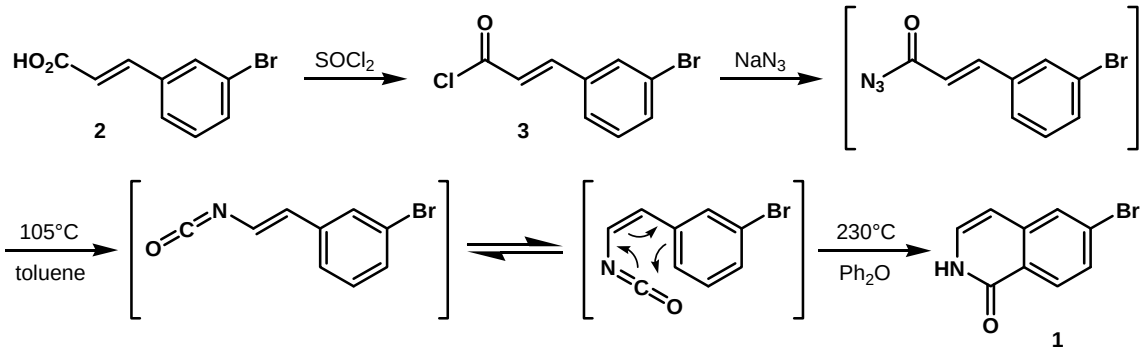
Abstract – During the preparation of 6-bromoisoquinolinone, a novel and unexpected reaction occurred to form a pyridinone and a pyrimidine-2,4-dione. We propose a [4+2] Diels-Alder dimerization of an intermediate styrene-isocyanate to explain the observed products.

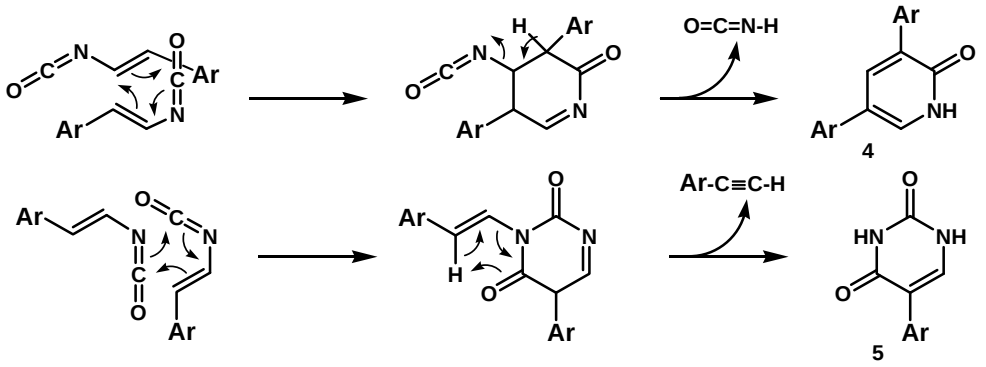
Heterocycles are among the most diverse organic moieties and as such are found in many important natural, agricultural, pharmaceutical, and industrial compounds. One such heterocycle of pharmaceutical interest is isoquinolinone. Isoquinolinones are reported as inhibitors of mGluR1, ROCK1, platelet ADP, 5-lipoxygenase, protein kinase B/Akt, and prostaglandin and leukotriene production, among others.[1]

During the course of our research we found it necessary to prepare 6-bromoisoquinolinone (**1**) as a key intermediate for further derivatization. Although syntheses of isoquinolinones using a modified Pomeranz-Fritsch reaction,[2] an S_NAr reaction,[3] and carbamate cyclization[4] have recently appeared, for expediency we followed the procedure by Sircar[5,6] for the preparation of a related isoquinolinone. 3-Bromocinnamic acid (**2**) was first converted to its acid chloride (**3**) with thionyl chloride. This intermediate was then reacted with sodium azide to give 3-bromocinnamoyl azide, which underwent a Curtius rearrangement to the isocyanate and cyclized to give the expected product **1**[7] upon further heating (Scheme 1). To our surprise, we also isolated two other intriguing compounds in the reaction mixture, and eventually identified them as 3,5-bis(3-bromophenyl)pyridinone (**4**)[8] and 5-(3-bromophenyl)uracil (**5**).[9]

A mechanistic rationale for the formation of both pyridinone **4** and uracil **5** is depicted in Scheme 2. They can be envisioned as [4+2] Diels-Alder adducts with subsequent loss of either cyanic acid or 3-bromophenylacetylene, followed by hydrogen migration. It would appear that these dimerizations are competitive with unimolecular cyclization since isomerization of the trans double bond to the cis geometrical isomer is not required. Besides being supported by the usual instrumental data (CHN, MS,



Scheme 1



Scheme 2 (Ar = 3-Br-C_6H_4)

IR, ^{1}HNMR, ^{13}CNMR), the proposed structures of both compounds are also supported by information gathered from further 2-D NMR experiments.

In the case of pyridinone **4**, proton assignments for the two aryl substituents can be easily grouped together using data from a COSY experiment. The coupling constant between the two remaining protons is 2.8 Hz, making them meta to one another. The phenyl groups can then be assigned on the basis of their ROESY cross peaks to these two protons on the pyridinone core (Figure); H-4 shows Overhauser effects to the ortho protons on both phenyl rings whereas H-6 only shows effects to those on one (besides the adjacent H-1). Using HSQC correlations, the proton assignments are readily transferred to their respective carbons, and the gHMBC data allows the quaternary carbons of the phenyl rings to be assigned based on the large meta H-C correlations to the already assigned protons. Additional gHMBC interactions between C-3 and H-4, and between C-5 and H-6, provide further support.

In the case of uracil **5**, HSQC correlations tie the protons to their respective carbons. ROESY cross peaks to H-6 are observed with H-1, the ortho protons of the phenyl ring, and H-3 (a relayed signal, not shown) (Figure). gHMBC cross peaks to H-6 are observed with carbonyl carbons C-2 and C-4, and with quaternary carbons C-5 and C-7; further cross peaks are seen between C-5 and the ortho protons of the phenyl ring. These correlations fix the position of the phenyl ring in relation to the lone uracil C-H. Further support for an adjacent nitrogen is seen in this carbon's downfield shift to 140.2 ppm.

We searched the literature for a precedent and found a citation for a Diels-Alder reaction with a similar substrate in a short paper published nearly forty years ago by Woerner and Reimlinger,[10] where they

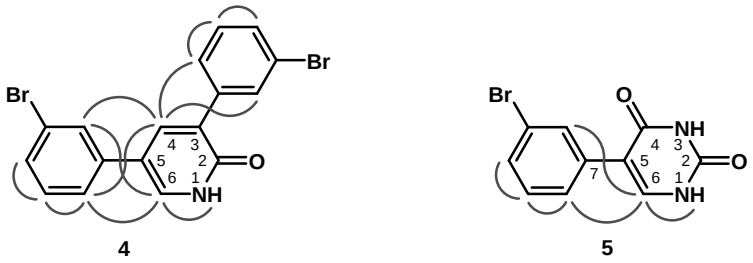
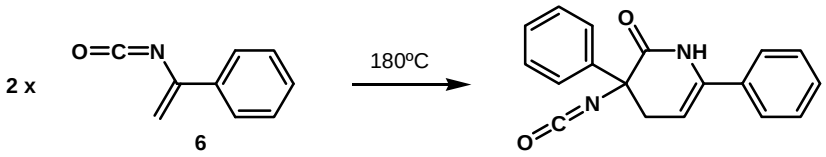


Figure (ROESY correlations)

describe the result of heating 1-isocyanatostyrene (**6**) at 180 ºC (Scheme 3). They found that no cyclization onto the phenyl ring occurred, but instead a dimerization in 40% yield, without elimination of cyanic acid.



Scheme 3

Although analogs of **4** and **5** itself have appeared in the literature,[11] to our knowledge this is the first time either heterocycle has been prepared through the intermediacy of an isocyanate as described here. Other pharmacologically important analogs of **4** and **5** have also appeared in the patent literature. 3,5-Diarylpyridinones have been claimed as AMPA receptor antagonists for the treatment of neurodegenerative diseases,[12] and 5-aryluracils were studied more than twenty years ago as potential pharmaceuticals in an East German patent,[13] and more recently as antagonists of serotonin 2, α_{1a} adrenergic, and gonadotropin-releasing receptors.[14]

In summary, we report the finding of a quick access to 6-bromoisoquinolinone, and the coincident finding of a route to potentially useful 3,5-diarylpyridinones and 5-aryluracils through a novel mechanistic pathway.

REFERENCES AND NOTES

1. H. Kawamoto, S. Ito, A. Satoh, Y. Nagatomi, Y. Hirata, T. Kimura, G. Suzuki, A. Sato, and H. Ohta, WO 2005/085214 A1; D. K. Drewry, D. K. Jung, J. A. Linn, R. N. Hunter III, D. Lee, R. A. Stavenger, and C. Sehon, WO 2005/074643 A2; R. M. Scarborough, H.-M. Jantzen, W. Huang, D. M. Sedlock, C. K. Marlowe, and K. A. Kane-Maguire, US 2002/077486 A1; J. H. Van Duzer and D. M. Roland, EP 526402 A1; K. W. Woods, J. P. Fischer, A. Claiborne, T. Li, S. A. Thomas, G.-D. Zhu, R. B. Diebold, X. Liu, Y. Shi, V. Klinghofer, E. K. Han, R. Guan, S. R. Magnone, E. F. Johnson, J. J. Bouska, A. M. Olson, R. de Jong, T. Oltersdorf, Y. Luo, S. H. Rosenberg, V. L. Giranda, and Q. Li, *Bioorg. Med. Chem.*, 2006, **14**, 6832; M. Shoda and H. Kuriyama, WO 2005/016862 A1.
2. E. R. Walker, S. Y. Leung, and A. G. M. Barrett, *Tetrahedron Lett.*, 2005, **46**, 6537.
3. R. J. Snow, T. Butz, A. Hammach, S. Kapadia, T. M. Morwick, A. S. Prokopowisc, H. Takahashi, J. D. Tan, M. A. Tschantz, and X.-J. Wang, *Tetrahedron Lett.,* 2002, **43**, 7553.

4. D. Ferraris, R. P. Ficco, T. Pahutski, S. Lautar, S. Huang, J. Zhang, and V. Kalish, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2513.
5. I. Sircar, S. J. Haleen, and S. E. Burke, *J. Med. Chem.,* 1992, **35**, 4442. For a similar method see also: S. Shkavrov, S. Popov, D. Kravchenko, and M. Krasavin, *Synth. Commun.*, 2005, **35**, 725.
6. 3-Bromocinnamic acid (5.22 g, 23 mmol) was mixed with thionyl chloride (5 mL), treated with a solution of pyridine (2 drops) in thionyl chloride (2 mL), and stirred overnight. Excess thionyl chloride was distilled off, and the residue concentrated twice more from dioxane. Then a solution of the intermediate acyl chloride in dioxane (10 mL) was added portionwise to a mixture of sodium azide (2.28 g, 35 mmol) in water (5 mL) and dioxane (5 mL) cooled in a water ice bath. After 20 min the bath was removed, the biphasic mixture was stirred thoroughly for 90 min at rt, and then cooled again to 0 ºC. Crushed ice and toluene (10 mL) were added, and the mixture was stirred until all the solids dissolved. The aqueous phase was separated and extracted with toluene, and the combined organic phases were washed with brine and dried (Na_2SO_4). The crude acyl azide was concentrated to about 20 mL (CAUTION: Do not concentrate to dryness as organic azides are potential explosion hazards), slowly heated to 105 ºC (nitrogen bubbles off), and kept at that temperature for 40 min. Then the solution of styrene-isocyanate was brought to rt and concentrated. The residue was diluted with diphenyl ether (10 mL), heated at 230 ºC for 20 min, concentrated under vacuum, and chromatographed on silica to give compounds **1**, **4**, and **5**.
7. 16% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.53 (d, J = 7.1 Hz, 1H), 7.23 (dd, J = 7.1, 5.8 Hz, 1H), 7.62 (dd, J = 8.5, 2.0 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 11.34 (bs, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 161.4 (C), 139.6 (C), 130.5 (CH), 129.2 (CH), 129.0 (CH), 128.3 (CH), 126.3 (C), 124.9 (C), 103.6 (CH); IR (cm^{-1}) 3023, 2857, 1666, 1637, 1597, 1241, 827, 790; MS (ESI, M+H$^+$) m/z 224, 226; HRMS calcd for C_9H_6BrNO+H$^+$ 223.97055, found 223.97098.
8. 9% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.37 (dd, J = 8.0, 8.0 Hz, 1H), 7.38 (dd, J = 8.0, 8.0 Hz, 1H), 7.49 (ddd, J = 8.0, 1.8, 0.9 Hz, 1H), 7.53 (ddd, J = 8.0, 1.8, 0.9 Hz, 1H), 7.70 (ddd, J ~ 7.7, 1.8, 0.9 Hz, 1H), 7.83-7.88 (m, 2H), 7.94 (dd, J = 1.8, 1.8 Hz, 1H), 8.08 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 1.8, 1.8 Hz, 1H), 12.26 (bs, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 160.4 (C), 138.7 (C), 138.6 (C), 138.0 (CH), 133.2 (CH), 130.9 (CH), 130.8 (CH), 130.1 (CH), 129.9 (CH), 129.5 (CH), 128.1 (CH), 128.0 (C), 127.4 (CH), 124.6 (CH), 122.4 (C), 121.2 (C), 116.8 (C); IR (cm^{-1}) 2859, 1650, 1594, 1561, 1481, 875; MS (ESI, M-H$^+$) m/z 402, 404, 406; HRMS calcd for $C_{17}H_{11}Br_2NO$+H$^+$ 403.92802, found 403.92834. Anal. Calcd for $C_{17}H_{11}Br_2NO$•0.25 H_2O: C, 49.85; H, 2.83; N, 3.42. Found C, 49.82; H, 2.61; N, 3.47.
9. 19% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.31, (ddd, J = 8.0, 7.8, 0.3 Hz, 1H), 7.46 (ddd, J = 8.0, 2.0, 1.1 Hz, 1H), 7.56 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H), 7.74 (s, 1H), 7.79 (ddd, J = 2.0, 1.7, 0.3 Hz,

1H), 11.25 (bs, 1H), 11.30 (bs, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 110.0 (C), 120.8 (C), 126.3 (CH), 129.1 (CH), 129.6 (CH), 129.8 (CH), 135.3 (C), 140.2 (CH), 150.4 (C), 162.5 (C); IR (cm^{-1}) 3177, 3079, 1747, 1682, 1451, 1234, 791, 694; MS (ESI, M-H^+) m/z 265, 267; HRMS calcd for $C_{10}H_7BrN_2O_2$-H^- 264.96181, found 264.96251. Anal. Calcd for $C_{10}H_7BrN_2O_2$: C, 44.97; H, 2.64; N, 10.49. Found C, 44.76; H, 2.38; N, 10.32.

10. F. P. Woerner and H. Reimlinger, *Chem. Industry*, 1971, **25**, 704.
11. A. Sutherland and T. Gallagher, *J. Org. Chem.*, 2003, **68**, 3352; U. Wellmar, A.-B. Hoernfeldt, and S. Gronowitz, *J. Heterocycl. Chem.,* 1995, **32**, 1159.
12. T. Smith, WO 2003/047577 A2.
13. J. Seres, K. Daroczi, P. Seres, and B. Koszegi, DD 222591 A5.
14. Y. Watanabe, H. Kakui, and T. Shibano, JP 03264579 A; J. B. Nerenberg, and M. G. Bock, WO 2000/029386 A1; Y.-F. Zhu, C. Chen, F. C. Tucci, Z. Guo, T. D. Gross, M. Rowbottom, and R. S. Struthers, WO 2001/055119 A2.