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OXIDATION OF AROMATIC BIS-AMIDES BY THALLIUM (III) TRIFLUOROACETATE

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Abstract: Aromatic 1,2-bisamides undergo thallium (III) promoted oxidative intramolecular cyclization to generate new 5-membered heterocyclic rings. Formation of para-quinone was shown to be a minor pathway in one case.

In the past decade, most of the work on organothallium chemistry has been carried out by McKillop and Taylor and coworkers, who are primarily responsible for the application of various thallium (III) reagents in organic synthesis.[1-4] In particular, enhancement of the electrophilic properties of thallium (III) trifluoroacetate (TTFA) relative to thallium (III) acetate, together with its ease of synthesis, makes it a convenient reactive thallation reagent. The products of thallation, arythallium di(trifluoroacetates), undergo a variety of substitution reactions yielding, for example, iodides,[5,6] fluorides,[7] nitriles,[8] thiophenols,[1] and phenols.[8]

The reactivity of TTFA as an oxidizing agent was exemplified by the conversion of phenols into para-quinones.[9,10] Oxidative non-phenolic coupling of aromatic compounds promoted by TTFA also provides a valuable access to natural products otherwise difficult to synthesize.[11,12] Treatment of a variety of aromatic compounds with TTFA in trifluoroacetic acid results in facile oxidative coupling to give symmetrical biaryls[13] via a radical cation mechanism.[14] Both oxygen and halogen functions on the aromatic substrates can be tolerated.

The high-yield conversion[13] of 4-bromoveratrole to 2,2'-dibromo-4,4',5,5'-tetramethoxybiphenyl by TTFA prompted us to investigate the thallium route for the conversion of 1,2-diacetamido-4-bromobenzene (I) to 2,2'-dibromo-4,4',5,5'-tetraacetamidobiphenyl (II). Organothallium chemistry of aromatic amides is not known. Instead of biaryl coupling, I underwent mononuclear oxidation in the presence of TTFA to yield 4-acetamido-6-bromo-2-methylbenzoxazole (III, 24%) and 2-acetamido-5-bromo-1,4-benzoquinone (IV, 3%).

In a typical reaction, TTFA (7.5 mmoles) was weighed out under argon and dissolved in 35 ml of trifluoroacetic acid. The solution was then quickly added to 15 mmoles of I under argon. The red-brown reaction mixture was stirred and heated at reflux (73°C) for 2 hours in the dark. Trifluoroacetic acid was partially removed by distillation and the concentrate poured into 200 ml of water. The aqueous mixture was then extracted with 4 x 50 ml of chloroform. The chloroform extracts were combined, washed with saturated aqueous sodium

bicarbonate and then with water, and dried over anhydrous magnesium sulfate. After solvent removal, the solid residue was extracted with ether to separate the soluble products from the unreacted starting material. The impure product mixture was then purified by silica gel column chromatography to give first pure IV in the chloroform eluate and then pure III in the 1:1 chloroform-ether eluate. No reaction occurred when the reactant mixture was stirred for 2 hours at 20 to 25°C. Extension of the reflux period to 24 hours did not increase the yields of products. When double the theoretical amount of TTFA was used, the yields were not increased, but there was a larger amount of highly colored impurities. Washing the chloroform extracts with saturated aqueous sodium bicarbonate was absolutely necessary, for no pure product was isolated when the washing was omitted.

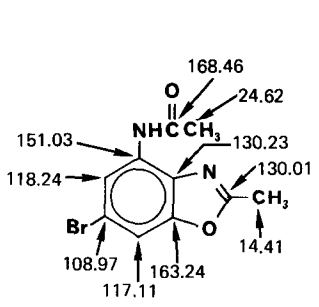
Compound III is a white crystalline solid, mp 160.5-162°C, which gave a positive Beilstein test; IR (KBr) 3300, 1680, 1630, 1530, 1400 and 1270 cm^{-1}; MS m/e 268, 270 (molecular ion); NMR ($CDCl_3$) δ 2.32 (s, 3H, $COCH_3$), 2.67 (s, 3H, CH_3–C=N–), 7.38 (d, 1H, J = 2 Hz, H_5), 8.15 (broad s, 1H, NH), and 8.48 ppm (d, 1H, J = 2 Hz, H_7). Anal. for $C_{10}H_9BrN_2O_2$: Calculated: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.50; H, 3.65; N, 10.21.

Compound IV crystallized from dichloromethane-hexane as lustrous golden platelets, mp 186°C, which also gave a positive Beilstein test; IR (KBr) 3300, 1700, 1670, 1640, 1590, 1510, and 1325 cm^{-1}; MS m/e 243, 245 (molecular ion); NMR ($CDCl_3$) δ 2.27 (s, 3H, $COCH_3$), 7.33 (s, 1H, H_6) 7.83 (s, 1H, H_3), and 8.00 ppm (broad s, 1H, NH). Anal. for $C_8H_6BrNO_3$: Calculated: C, 39.37; H, 2.48; N, 5.74; Br, 32.74. Found: C, 39.35; H, 2.50; N, 5.71; Br, 33.10.

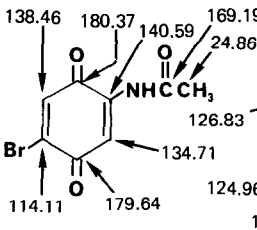
The poor material balance (>70% of the organics could not be retrieved from the aqueous solution even after repetitive extractions with chloroform) was probably due to strong complexation of the acetamido groups with TTFA. Tosylation (instead of acetylation) of the amine functions on 4-bromo-1,2-diaminobenzene was expected to suppress the complexation with thallium on both steric and electronic grounds. Consequently, 1,2-bis (4-tolylsulfonamido)-4-bromobenzene was synthesized[15] and allowed to react with TTFA.

The crystalline product (mp 215-216°C) gave a positive Beilstein test and was identified as 7-bromo-2-(4-tolyl)-4-(4-tolyl)sulfonamido-1,2,3-benzoxathiazole 2-oxide (V): 70% yield; IR (KBr) 3460, 1610, 1500, 1340, and 1175 cm^{-1}; MS m/e 492, 494 (molecular ion); NMR (DMSO-d_6) δ 2.36 (s, 6H, CH_3), 6.75-7.80 (m, 10H, aromatic) and 9.30 ppm (broad s, 1H, NH). Anal. for $C_{20}H_{17}BrN_2O_4S_2$: Calculated: C, 48.69; H, 3.52; Br, 16.20; N, 5.68; S, 13.00. Found: C, 48.37; H, 3.86; Br, 15.97; N, 5.57; S, 13.01.

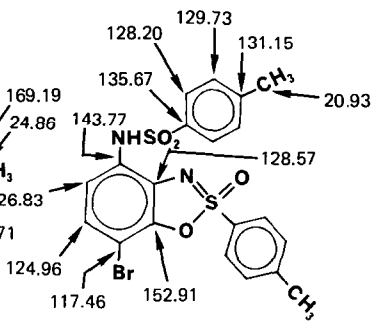
Carbon-13 NMR spectral characteristics[16] for compounds III, IV and V are consistent with the assigned structures (see diagram).



(III)



(IV)



(V)

The results reported herein are first examples of an oxidative intramolecular cyclization pathway[17] of aromatic amides in the presence of TTFA. The synthetic utility of this reaction and the mechanistic details await further research. We do not intend to continue this pursuit, however.

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14. E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, J. Org. Chem., 43, 3632 (1978).
15. This compound was synthesized by ditosylation of o-phenylenediamine (78% yield), followed by bromination of 1,2-bis(4-tolylsulfonamido)benzene in glacial acetic acid at 90°C (54% yield): mp 196-199°C; Anal. for $C_{20}H_{19}BrN_2O_4S_2$: Calculated: C, 48.48; H, 3.87; Br, 16.13; N, 5.66; S, 12.94. Found: C, 49.41; H, 3.98; Br, 16.12; N, 5.74; S, 13.28.
16. The chemical shift values are downfield from TMS internal standard. The solvent used for III and IV was $CDCl_3$ and for V, DMSO-d_6.
17. A novel TTFA-promoted oxidative intramolecular cyclization of alicyclic dicarboxylic acids has been reported recently: E. C. Taylor, G. E. Jagdmann, Jr., and A. McKillop, J. Org. Chem., 45, 3373 (1980).

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