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Iodination and Metal Halogen Exchange of Aromatic Compounds: An Improved Preparation of a Key Oxazolidinone Antibiotic Intermediate

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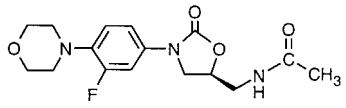
Abstract:

A new method for the preparation of a key intermediate for oxazolidinone antibiotic analogues is discussed. We have found that iodine−magnesium exchange can be used to prepare a dianion if a fluorine is present ortho to the aryl anion and that exchange takes place on iodoanisoles. In addition, we report an improved method for iodination of aromatics using *N*-chlorosuccinimide/hydriodic acid and potassium iodide. By using these conditions, reactions are faster and higher-yielding than using either *N*-iodosuccinimide or iodine monochloride.

Linezolid (**1**), the first representative of a new class of oxazolidinone antibacterials, is indicated as a hospital-use antibiotic for treatment of serious gram-positive pathogens (*Staphylococci*, *Streptococci*, and *Entercocci*) implicated in skin and soft tissue infections, pneumonias, and bacteremias.[1] Oxazolidinones containing carbon−aryl bonds, such as compound **2**, in place of the nitrogen−aryl bond of linezolid are also active as antibacterials.[2] To examine the properties of these products it is important to develop high-yielding methods for their preparation. One of the critical synthetic challenges involved in approaching these compounds is the formation of the carbon−carbon bond linking the fluorinated aromatic ring with the sulfur heterocycle.



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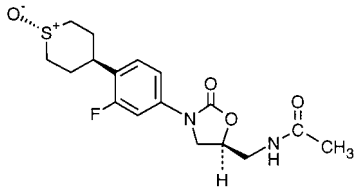
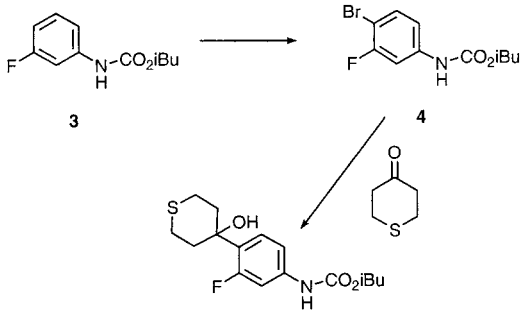


2

In a previous report, lithium−bromine exchange on the carbamate, **4**, followed by addition of magnesium salts provided an aryl−magnesium species, which was reacted with tetrahydrothiopyran-4-one to provide the desired intermediate, **5**.[3] This intermediate can then be converted to oxazolidinones such as **2** using chloropropanediol and alkoxide. This procedure was dilute and long, requiring the in situ preparation of anhydrous magnesium salts. Therefore, we sought to improve this conversion by a direct magnesium−halogen exchange reaction on the aryl iodide. Direct magnesium−halogen exchange on the bromide could not be effected, however we felt that the aryl iodide could possibly undergo exchange.



3 4 5

Acylation of 3-fluoroaniline with isobutylchloroformate under Schotten−Baumann conditions proceeded smoothly to provide the carbamate **3** in 96% yield. Preparation of the aryl iodide was achieved by electrophilic iodination of the isobutyl carbamate.[4] Reaction of the crystalline carbamate with *N*-iodosuccinimide was slow and required more than 48 h to reach completion giving an 86:14 mixture of the ortho and para-iodo products, **7** and **8**.[5] Crystallization of the product from ethyl acetate or heptane provided only the desired ortho isomer **7** in 57% isolated yield. If the crude methylene chloride solution from acylation was used without isolation, the iodination reaction was complete in less than 24 h. We suspected that carry-over of some inorganic material was responsible for this and found that addition of 1−10 mol % of chloride ion accelerates the reaction when using isolated carbamate. The ratio of ortho to para reaction products was not affected by this catalysis, but the reaction was complete in less than 6 h at 25 °C to give the desired ortho product in 72% isolated yield. The catalytic effect is

(1) Brickner, S. J.; Hutchinson. D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673−679.

(2) Poel, TJ.; Martin, J. P., Jr.; Barbachyn, M. R. PCT Int. Appl. WO Patent 9929688, 1999; *Chem. Abstr.* **1999**, *131*, 31934.

(3) Gage, J. R.; Perrault, W. R.; Poel, T. J.; Thomas, R. C. *Tetrahedron Lett.* **2000**, *41*, 4301−4305.

(4) For a review of iodination of aromatics, see: Merkushev, E. B. *Synthesis* **1988**, 923.

(5) Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993** *58*, 3194; Orazi, O. O.; Corral, R. A.; Bertarello, H. E. *J. Org. Chem.* **1965** *30*, 1101.

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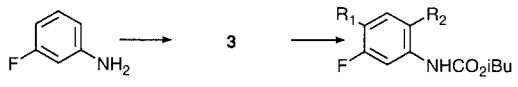
substantial early in the reaction, but diminishes as the reaction approaches completion, suggesting the presence of a catalytic species that is consumed or poisoned during the course of the reaction. The counterion for the added halogen has a limited effect. The group 1A metals are indistinguishable from each other, but tetrabutylammonium and ammonium salts accelerate the reaction to a much greater extent and lead to over-reaction products in some cases. This may be due to a phase-transfer effect in the methylene chloride/water solvent system. When bromide ion was added, the bromide product was formed in an amount corresponding to the amount of bromide catalyst added, suggesting that a mixed halogen species such as ICl or IBr was being generated in situ.

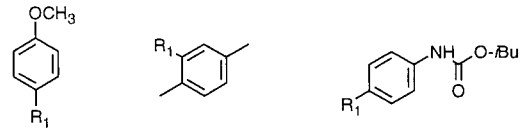


6

7 $R_1 = I$, $R_2 = H$
8 $R_1 = H$, $R_2 = I$

If we were indeed generating mixed halogens, we theorized we would be able to iodinate with *N*-chlorosuccinimide (NCS) and iodide. The reaction of **3** with *N*-chlorosuccinimide and potassium iodide provided only the iodide in a 56% yield.[6] Using hydriodic acid as the iodide source, **7** was obtained in a 78% isolated yield after overnight at room temperature. This result was comparable to the use of *N*-iodosuccinimide and potassium chloride. The optimized conditions were found to be 1.5 equiv of *N*-chlorosuccinimide, 0.5 equiv of HI (57% aqueous), and 1.0 equiv of KI in methylene chloride and water at 20−35 °C. Under these conditions we were able to convert **6** to **7** in an overall yield of 79%. Due to the lower cost of positive chlorine (NCS) species versus positive iodine (NIS, ICl) species, this iodination procedure represents a less expensive way to introduce iodine into aromatic nuclei. Attempts to replace the NCS in this system with either $NaClO_2$ or chloramine-B hydrate were unsuccessful.

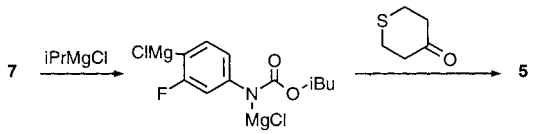
We applied the NCS/HI/KI iodination conditions to several other substrates, and we found that these conditions are general for electron-rich substrates, but that electron-deficient rings do not react. Anisole, **9**, *p*-xylene, **10**, and the des-fluoro carbamate, **11**, were reacted under these conditions to provide the monoiodination products, **12**, **13**, and **14** in 72−94% yield. Reactions on these substrates under the NCS/KI/HI conditions were complete 2−3 times faster than reactions on the same substrates with *N*-iodosuccinimide without catalyst. We also found that 3-fluoroaniline did not give any of the desired iodinated products under these reaction conditions. This was rather unexpected, as similar methods are reported to work for anilines.[7]



9 $R_1 = H$ **10** $R_1 = H$ **11** $R_1 = H$
12 $R_1 = I$ **13** $R_1 = I$ **14** $R_1 = I$

Adapting the chemistry of Knochel et. al.,[8] metalation of **7** using *iso*-propylmagnesium chloride was explored as an alternate means for generating the aryl magnesium.

We found that metalation of **7** could be effected at −40 °C in 2−3 h with 2.1 equiv of *iso*-propylmagnesium chloride in THF. Formation of the carbamate anion was fast at this temperature, with iodine−magnesium exchange being the rate-limiting reaction. The exchange was much faster (<1 h) at −25 °C. We observed no formation of benzyne-derived products when the reaction temperature was kept below −15 °C.



Addition of a THF solution of the tetrahydrothiopyran-4-one to the dianion resulted in a rapid addition reaction to provide the desired tertiary alcohol, **5** in 63% isolated yield. The major byproducts are **3**, which results from proton transfer from the ketone, and the aldol addition product of the resulting ketone enolate with another molecule of ketone.

Use of additives and cosolvents were explored to help minimize the proton transfer. Addition of copper(I) iodide or cerium(III) chloride resulted in poor yields while adding 3 mol equiv of TMEDA increased the yields to 80−90%. Use of more TMEDA did not show a continued increase in yield. Use of less than 3 equiv of TMEDA gave yields in the 65−70% range. We conducted experiments in which the TMEDA was added before transmetalation, after transmetalation but before thiopyranone addition, and without TMEDA. There were no significant differences in the yield of the first two experiments, indicating that the TMEDA does not likely play a role in the iodine−magnesium transfer. However, the experiment without TMEDA gave a lower isolated yield (63% vs 84%), indicating that TMEDA has a role in the addition reaction. Examination of the reaction byproducts of the experiments shows that less proton transfer takes place when TMEDA is present.

We have found that the addition is very rapid and that warming the reaction before quenching is detrimental to the yield and purity. We prefer to quench the addition reaction within 30 min of the thiopyranone addition at −25 °C by adding acetic acid and then warming the reaction mixture. Warming the reaction mixture before quenching promotes the aldol condensation of the excess tetrahydrothiopyran-4-one and reduces the product purity.

The tertiary alcohol product can be transformed into a variety of oxazolidinones using the methodology described in the previous report.[3]

(6) This reaction is known for radio labeling using I-125; (a) Wilson, A. A.; Dannals, R. F.; Ravert, H. T.; Burns, H. D.; Wagner, H. N., Jr. *J. Labeled Comput. Radiopharm.* **1986**, *23*, 83 (b) Youfeng, H.; Coenen, H. H.; Petzold, G.; Stocklin, G. *J. Labeled Comput. Radiopharm.* **1982**, *19*, 807; (c) Ponchant, M.; Koscielniak, T.; Hamon, M.; Gozlan, H. *J. Labeled Comput. Radiopharm.* **1991**, *29*, 1147.

(7) Edgar, K. J.; Falling, S. N. J. *Org. Chem.* **1990**, *55*, 5287−5291.

(8) Roymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701−1703.

The direct metalation of **7** was surprising because the previously cited examples were all activated aromatics.[8] The transmetalation chemistry was also examined with *p*-iodoanisole, **12**, iodoxylene **13**, and the des-fluoro compound **14**. The resulting anions were trapped with either benzaldehyde or tetrahydothiopyran-4-one.

In the case of **12**, the reaction proceeded using either carbonyl compound; however, the temperature had to be raised to greater than 0 °C for iodine−magnesium exchange to occur. The isolated yields were lower in these reactions than in the case of **7**. This was attributable, in part, to incomplete iodine−magnesium exchange on a less activated ring system and in part to an increased level of side products that were formed at higher temperatures. Attempts to react compounds **13** and **14** were unsuccessful. Little iodine exchange was observed, and quenching with benzaldehyde did not give any of the desired secondary alcohol adduct.

In summary, we have found that iodine−magnesium exchange can take place on aromatics without strong activating groups and can be used to prepare a dianion. In addition we report an improved method for iodination of aromatics using NCS/HI/KI.

Experimental Section

General Procedures. All reagents were commercially obtained and used as received unless otherwise noted. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids or solutions were transferred via syringe or polypropylene cannula. Organic solutions were concentrated by rotary evaporation at ~80 mmHg and less than 60 °C except where noted. Chromatographic purification of products was accomplished using forced-flow chromatography on EM Silica Gel 60. Thin-layer chromatography was performed on Analtech Chromatography Products Uniplate Silica Gel GF 0.25 mm plates. Visualization of the developed chromatogram was performed by fluorescence quenching or phosphomolybdic acid (PMA) stain or 50% sulfuric acid char.

NMR spectra were measured on a Bruker AM-400 operated at 400 and 100 MHz, for ^{1}H and ^{13}C, respectively, with data reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration and coupling constant (J, Hz). ^{1}H−^{13}C Multiplicities are reported on the basis of DEPT data. Where ^{13}C−^{19}F coupling occurs, the coupling constant (J_{C-F}) is reported. Elemental analyses were obtained from Pharmacia and Upjohn Physical and Analytical Chemistry. HPLC analyses were carried out on a Dionex DX 500 Chromatography System. GC analyses were carried out with a Hewlett-Packard 5890a gas chromatograph.

Preparation of 7 from 6. To a solution of 3-fluoroaniline, **6**, (50.0 g, 450 mmol) in methylene chloride (200 mL) was added a solution of potassium carbonate (46.9 g, 339 mmol) in water (200 mL) at room temperature. The mixture was warmed to 32 °C, and isobutyl chloroformate (66.2 g, 485 mmol) was added over 13 min while maintaining 30−35 °C. The mixture was stirred at 30−35 °C for 2.5 h until complete by GC analysis. Aqueous ammonia (29.3 wt %, 7.2 mL, 111 mmol) was added and the mixture stirred at 30−35 °C for 15 min. The mixture was cooled to 25 °C and the pH adjusted from 8.7 to 1.9 with concentrated hydrochloric acid. The phases were separated, and the aqueous was washed with methylene chloride (100 mL). The combined organics were washed with water (200 mL), and the water wash was back-extracted with methylene chloride (100 mL). [If desired, crystallization at this point from heptane at −30 °C afforded **3** in 98.1% yield.] To a 1 L three-neck round-bottom flask was charged potassium iodide (52.3 g, 315 mmol), *N*-chlorosuccinimide (102.2 g, 765 mmol), and 450 mL of water. The mixture was heated to 32 °C. A light green suspension resulted. Hydriodic acid (47%, 29.7 mL, 225 mmol, 0.5 equiv) was added, which turned the mixture purple, and the slurry nearly went into solution. A 5 °C exotherm was observed. The solution of **3** in methylene chloride was added and the mixture stirred at 32 °C until the reaction was complete by HPLC. Reaction was complete after 3 h. The solution turned from a dark purple to a light orange throughout the reaction.

The mixture was cooled to 23 °C and quenched by adding a solution of 57.0 g of sodium sulfite in 340 mL of water over 5 min, keeping the temperature less than 33 °C. The solution immediately turned to a dark purple at the start of the quench, then to a light yellow by the end of the quench. The layers were separated, and the upper aqueous layer was extracted with 120 mL of methylene chloride. The combined organics were washed with 120 mL of water. The layers were separated, and the aqueous was washed with 50 mL of methylene chloride. The combined organics were concentrated to a 250 mL volume (solids present) on the rotovap, and 500 mL of octane was added (more crystals formed). The slurry was concentrated to 350 mL on the rorovap. The slurry was very thick. Octane (200 mL) was added to the slurry and the mixture cooled to 0 °C. The slurry was filtered on a 600 mL sintered glass funnel and washed with 2 × 100 mL of octane pre-cooled to less than 10 °C. The filtration rate was very fast. The solids were dried in a vacuum oven overnight at 55 °C. This yielded 109.5 g of **7**, as off-white fluffy solids.

3: mp 62−63 °C; TLC R_f = 0.34 (5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, 1H, J = 11.0), 7.22 (q, 1H, J = 8.4), 7.03 (d, 1H, J = 8.1), 6.86 (bs, 1H), 6.74 (td, 1H, J = 2.3, 8.3), 3.95 (d, 2H, J = 6.7), 1.97 (nonet, 1H, J = 6.7), 0.96 (d, 6H, J = 6.7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.21 (ds, J_{C-F} = 244.6), 153.58 (s), 139.71 (ds, J_{C-F} = 10.6), 130.10 (dd, J_{C-F} = 9.8), 113.90 (d), 109.96 (dd, J_{C-F} = 21.1), 106.05 (dd, J_{C-F} = 27.9), 71.59 (t), 27.95 (d), 19.03 (q); MS (CI, NH_3) *m/z* (relative intensity) 230 (10), 229 (100), 213 (2.7), 212 (25), 211 (7.7). Anal. Calcd for $C_{11}H_{14}FNO_2$: C, 62.55; H, 6.68; N, 6.63. Found: C, 62.65; H, 6.76; N, 6.67.

7: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (t, 2H, J = 8.4), 6.96 (dd, 1H, J = 2.0, 8.4), 6.87 (bs, 1H), 3.96 (d, 2H, J = 6.4), 1.97 (nonet, 1H, J = 13.5), 0.96 (d, 6H, J = 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.24 (ds, J_{C-F} = 245.5), 153.39 (s), 138.98 (ds, J_{C-F} = 10.1), 133.33 (d), 115.10 (d), 107.08 (dd, J_{C-F} = 28.2), 102.03 (ds, J_{C-F} = 21.1), 71.78 (t), 27.92

(d), 19.01 (q). Anal. Calcd for $C_{11}H_{13}FINO_2$: C, 39.16; H, 3.90; N, 4.15; I, 37.64. Found: C, 39.25; H, 3.86; N, 4.17; I, 37.64.

Preparation of 5 from 7. To a 250 mL three-necked round-bottom flask equipped with a mechanical stirrer, thermocouple, and nitrogen purge was added **7** (10.0 g, 29.6 mmol), THF (60 mL), and TMEDA (10.3 g/13.4 mL, 88.9 mmol). The resulting solution was cooled to −25 °C, and isopropylmagnesium chloride (31.4 mL, 2 M, 62.8 mmol) was added via add funnel over 15 min, keeping the temperature less than −25 °C. The solution turned from a light yellow to a light brown color during the addition. The solution was stirred at −25 °C for 20 min and then sampled for HPLC. HPLC showed complete reaction of the idodide. Tetrahydrothiopyran-4-one (4.8 g, 41.5 mmol) was dissolved in 12 mL of THF and added dropwise to the reaction mixture over 10 min, keeping the temperature less than −20 °C. A 7 °C exotherm was observed during the addition. The mixture was stirred at −20 °C for 1 h. The reaction was quenched by addition of the reaction mixture all at once into a mixture of 13 mL of glacial acetic acid and 66 mL of water. The quench was started at 0 °C, and the temperature rose to 27 °C. MTBE (25 mL) was added and the mixture stirred for 20 min. The layers were separated, and the lower aqueous layer was washed with 25 mL of MTBE. The separation was not very clear; thus, 15 mL of octane was added which gave a clear phase break. The combined organics were washed with 25 mL of saturated ammonium chloride. The layers were separated, and the lower aqueous phase was washed with 25 mL of MTBE. The combined organics were concentrated to a 50 mL volume via rotovap. Octane (50 mL) was added and the solution concentrated to 50 mL (the product oiled out). The mixture was cooled to 23 °C (solids formed on cooling) and the solids filtered on a 60 mL coarse sintered glass funnel using house vacuum. The filtration rate was very fast. The solids were washed with 2 × 25 mL octane and pulled dry with vacuum. The product was then dried in the vacuum oven overnight at 40 °C. This provided 9.4 g of **5** as off white solids, a 96% yield. The solids contained about 10% of the thiopyranone dimer for a corrected yield of 86%. Recrystallization of the material from ethyl acetate provided an analytically pure sample.

7: mp 148−151 °C; TLC R_f = 0.35 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (t, 1H, J = 8.8), 7.32 (d, 1H, J = 14.4), 7.00 (dd, 1H, J = 1.6, 8.4), 6.74 (bs, 1H), 3.96 (d, 2H, J = 6.4), 3.23 (t, 2H, J = 12.8), 2.44 (d, 2H, J = 14.0), 2.37 (td, 2H, J = 3.6, 13.6), 2.05 (d, 2H, J = 14.4), 1.96 (nonet, 1H, J = 6.8), 0.96 (d, 6H, J = 6.8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.28 (ds, J_{C-F} = 243.0), 153.49 (s), 138.71 (ds, J_{C-F} =12.0), 129.93 (ds, J_{C-F} = 44), 126.67 (dd, J_{C-F} = 6), 113.85 (d), 107.03 (dd, J_{C-F} = 29.4), 71.65 (d), 71.24 (ds, J_{C-F} = 4.0), 37.67 (t), 37.64 (t), 27.95 (d), 23.90 (t), 19.03 (q); MS (CI, NH_3) *m/z* (relative intensity) 327 (7.0), 312 (6.4), 311 (17), 310 (100). Anal. Calcd for $C_{16}H_{22}FNO_3S$: C, 58.69; H, 6.77; N, 4.28. Found: C, 58.39; H, 6.68; N, 4.27.

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