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## Aromatization of Cyclohexenones with Iodine/sodium alkoxide. A Regioselective synthesis of 2-Iodophenols

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**Abstract:** Aromatizations of a wide variety of easily accessible 2-cyclohexenone-4carboxylates with iodine and sodium ethoxide give the corresponding 2-iodophenols in good yield and high regioselectivity.

2-Iodophenols are versatile building blocks for the synthesis of a variety of benzoheterocyclic systems. Palladium catalyzed annulations and carbonylative cyclizations of these materials with dienes and acetylenes have been widely utilized for the synthesis of biologically important heterocycles such as benzofurans,<sup>1</sup> dihydrobenzofurans,<sup>2,3</sup> benzopyrans,<sup>3</sup> flavones and chromones.<sup>4</sup> Although simple 2-iodophenols are readily accessible, methods for the regioselective preparation of more highly substituted analogues are quite limited. Direct iodination of substituted phenols with iodine-thallium(I) acetate has been reported to yield 2-iodophenols regioselectively in a few instances.<sup>5</sup> However, the yields of desired products are generally low as a result of competing diiodination. Herein we report that the aromatization reactions of a wide variety of easily accessible 3- or 5-substituted 2-cyclohexenone-4-carboxylates with iodine and sodium ethoxide give 2-iodophenols in good yields and high regioselectivity (equations 1 and 2).



3- and 5-substituted 2-cyclohexenone-4-carboxylates **1a-h** were readily prepared using previously reported procedures.<sup>6,7</sup> Treatment of compounds **1a-h** with 6 equivalents of sodium ethoxide in ethanol followed by slow addition of 2 equivalents of iodine at -78 °C gave 50-86% isolated yields of 2-iodophenols **2a-h** as a single regioisomer<sup>8</sup> in each case (Table 1).<sup>9,10</sup>

Entry	Cyclohexenone Substrate	Iodophenol Product		Yield (%)
1	EtO <sub>2</sub> C Me	EtO2C	2a	66
2	EtO <sub>2</sub> C F <sub>3</sub> C 1b	EtO <sub>2</sub> C	2b	86
3	EtO <sub>2</sub> C EtO <sub>2</sub> C 1c	EtO <sub>2</sub> C	2c	77
4	$EtO_2C$ O S Id	EtO <sub>2</sub> C OH	2d	61
5	EtO <sub>2</sub> C 1e	EtO <sub>2</sub> C OH	2e	50
6	EtO <sub>2</sub> C Me O If	EtO <sub>2</sub> C Me	2f	78
7	$F_{3C}$ $f$	F <sub>3</sub> C OH	2g	65
8	EtO <sub>2</sub> C Ph 0 1h	EtO <sub>2</sub> C Ph OH	2h	64

Table 1. Preparation of 2-Iodophenols from Cyclohexenones

Crude products from these reactions generally contained small amounts of 2,6-diiodophenols (3-5%) and non-iodinated phenols (3-5%) as byproducts which were readily removed by preparative LC. Low reaction temperature was critical in suppressing the byproduct formation. For example, iodination at room temperature gave 40-50% of monoiodophenols, 20-25% of diiodophenols and 20-25% of non-iodinated phenols. Although the reaction can accommodate a variety of substituents such as alkyl, aryl, heterocyclyl, trifluoromethyl and ester groups in the 3- or 5-position (Table 1), it appears to be limited to 2-cyclohexenones with an electron withdrawing substituent in the 4-position. For example, dione 3 and bicyclic imide 5 gave the expected iodophenols 4 and 6 in 56% and 84% isolated yields, respectively (equations 3 and 4). However, simple cyclohexenones such as 3-methyl-2-cyclohexenone, 3-phenyl-2-cyclohexenone and 3,4-dimethyl-2-cyclohexenone gave mostly unreacted starting material and small amounts of unidentified non-aromatic products.



The reaction most likely proceeds via anionic diiodination of cyclohexenones **1a-h** and subsequent dehydroiodination and aromatization. The formation of a thermodynamically more stable linearly conjugated dienolate 7 accounts for the regioselectivity. Although there are two possible diiodo intermediates **8a** ( $\alpha$ ,  $\alpha$ ) and **8b** ( $\alpha$ ,  $\gamma$ ), both of these structures provide the same iodophenol upon dehydroiodination and aromatization. The non-iodinated phenol and the diiodophenol byproducts may result from competing mono- and triiodinations of enolate **7** and subsequent dehydroiodination.



In summary, the iodinative aromatization described herein provides a convenient and highly regioselective *de novo* synthesis of 2-iodophenols with multiple substituents. The application of these iodophenol intermediates in the preparation of highly substituted benzoheterocyclic systems is currently in progress.

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- 5-Substituted 2-cyclohexenones 1a-e were prepared by Diels-Alder reaction of Danishefsky's diene with β-substituted acrylates followed by treatment of the adducts with trimethylsilyl triflate as reported previously: Vorndam, P. E. J. Org. Chem. 1990, 55, 3693-3695.



- 3-Substituted 2-cyclohexenones 1f-h were prepared by Robinson annulation reaction of the appropriate β-ketoesters with methyl vinyl ketone as reported previously: (a) Begue, J-P.; Bonnet-Delpon, D.; Dogbeavou, A. Synthetic Commun. 1992, 22, 573-579. (b) Walker, G. N. J. Am.Chem.Soc. 1955, 77, 3664-3667.
- 8. Regiochemistry of iodophenols 2a-h were readily determined by the coupling of aromatic proton resonances in <sup>1</sup>H nmr spectra. Compounds 2a-e exhibited singlets for the two phenyl protons. By contrast, the phenyl protons in compounds 2f-h showed two doublets with coupling constants of 7.0-8.4 Hz consistent with ortho coupling.
- 9. Representative procedure: To a solution of NaOEt (0.15 mol) in EtOH (80 mL) at -78 °C was added 6 g (0.025 mol) of cyclohexenone 1b. After 15 min, 12.7 g (0.05 mol) of iodine was added in small portions and the reaction mixture was stirred at -78 °C for 3 h and then at room temperature overnight. The reaction mixture was acidified with 5% HCl, the solvent was evaporated and the residue was dissolved in 1:1 H2O/EtOAc mixture. The organic layer was washed with satd.Na2S2O3, dried (MgSO4) and evaporated. Purification of the crude product by preparative LC (EtOAc/hexanes 1:4) gave 7.75 g (86%) of iodophenol 2b as a white solid: mp 136-138 °C.
- All new compounds gave satisfactory elemental analyses (C, H) and spectroscopic data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, MS).

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