



# Iodolactonization and iodoetherification of $\beta,\gamma$ -unsaturated acids and alcohols using $\text{FeCl}_3$ and NaI

Subhash P. Chavan\* and Anil K. Sharma

*Division of Organic Chemistry, Technology National Chemical Laboratory, Pune 411008, India*

Received 11 January 2001; revised 14 May 2001; accepted 23 May 2001

**Abstract**— $\beta,\gamma$ -Unsaturated alcohols and carboxylic acids undergo smooth iodoetherification and iodolactonization, respectively, using  $\text{FeCl}_3$  and NaI in acetonitrile in high yields and with short reaction times. © 2001 Elsevier Science Ltd. All rights reserved.

Iodolactonization and iodoetherification are crucial reactions in organic synthesis as well as in structure elucidation. Iodolactonization was utilized elegantly for stereoselective functional group incorporation and manipulation in Corey's prostaglandin synthesis<sup>1</sup> as well as in total syntheses of tumor inhibitors e.g. vernolepin and vernomenin<sup>2</sup> and in vitamin D<sub>2</sub> and D<sub>3</sub><sup>3</sup> synthesis. Likewise iodoetherification has been used in important organic syntheses e.g. of prostacyclin.<sup>4</sup> Iodolactonization and iodoetherification, are also of importance in structure determination, e.g. of isomeric mixtures, *endo* isomers give a quantitative yield of iodolactones and iodoethers, respectively, whereas, *exo* isomers are inert thus enabling the proportions of *endo* and *exo* isomers to be determined.

The conversion of  $\beta,\gamma$ - or  $\gamma,\delta$ -unsaturated acids into iodolactones was first reported by Bougault<sup>5</sup> who dissolved the unsaturated acid in aq.  $\text{NaHCO}_3$  and treated the solution with a solution of  $\text{I}_2$  in KI. A number of other methods are also in the literature for iodolactonization and iodoetherification e.g. the use of cyanogen iodide,<sup>6</sup>  $\text{Pb(IV)/NaI}$ ,<sup>7</sup> *N*-iodosuccinimide,<sup>8</sup>  $\text{I(collidine)}_2^+$ ,  $\text{ClO}_4^-$ ,<sup>9</sup>  $\text{Na}_2\text{S}_2\text{O}_8$ <sup>10</sup> etc. The standard iodolactonization procedure requires substantial quantities of potassium iodide and iodine together with long reaction times. We have developed a new approach to generate the intermediate iodonium ion using NaI with  $\text{FeCl}_3$  as the oxidant. It is pertinent to mention that

$\text{FeCl}_3/\text{NaI}$  combination has been used in halogen exchange reactions.<sup>11</sup>

In order to establish the efficacy and generality of this procedure, we subjected a variety of olefinic acids/alcohols to the reaction conditions. Good to excellent yields of iodoetherification and iodolactonization products were observed. The results are summarized in Table 1. A noteworthy feature of cyclization of the cyclic olefin in entry 6 is the exclusive formation of the butenolide, presumably arising from the elimination of the initially formed iodolactone under the reaction conditions. In order to confirm the formation of the butenolide, it was synthesized unambiguously by a method<sup>12</sup> previously developed by us.

Thus, we have established  $\text{FeCl}_3/\text{NaI}$  as an efficient reagent to effect iodolactonization as well as iodoetherification. The efficiency, generality and ease of operation of the present protocol will make it useful for the practicing organic chemist.

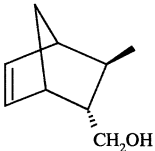
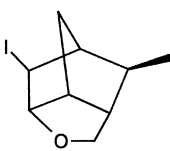
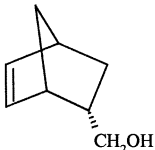
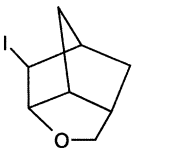
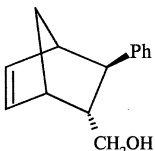
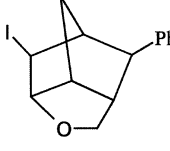
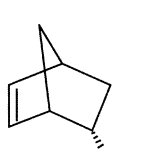
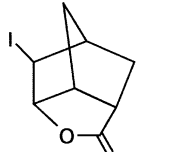
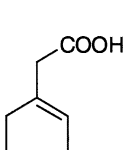
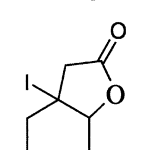
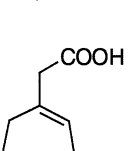
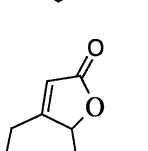
## General Procedure

To 2 mmol of the  $\beta,\gamma$ -unsaturated alcohol or acid was added 4 mmol of anhydrous  $\text{FeCl}_3$  and 4 mmol of NaI in 25 ml of acetonitrile. The solution was refluxed for 4–6 h. The reaction was then cooled, quenched with water and extracted with 3×20 ml portions of dichloromethane. The organic solution was then successively washed with 25 ml sat. aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , 25 ml of brine and finally with 25 ml of water. The organic solvent was removed on a rotary evaporator under reduced pressure and the residue thus obtained purified by column chromatography ( $\text{SiO}_2$ ) to furnish the iodoethers and iodolactones.<sup>13</sup>

**Keywords:** etherification; lactonization; olefins; alcohols; carboxylic acids.

\* Corresponding author. Fax: +91-20-5893614; e-mail: spchavan@dalton.ncl.res.in

**Table 1.** FeCl<sub>3</sub>/NaI mediated idoetherification and idoesterification

entry	substrate	product	yield (%)
1.			100
2.			94
3.			93
4.			86
5.			76
6.			75

### Acknowledgements

One of us (A.K.S.), thanks the CSIR, New Delhi (India) for the award of a fellowship. Funding under the YSA scheme from CSIR, India is gratefully acknowledged. We are thankful to Dr. M. K. Gurjar, Head and Dr. T. Ravindranathan Ex. Head Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411008, India for encouragement.

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- Spectral data for 2-iodo-9-methyl-4-oxa tricyclo[4.2.1.0<sup>3,7</sup>]nonane (entry 1, Table 1). <sup>1</sup>H NMR (200 MHz) δ: 1.07 (d, 3H J=7 Hz), 1.48 (m, 1H), 1.85 (m, 1H), 1.95 (br s, 1H), 2.1 (d, 2H J=7 Hz), 2.58 (m, 1H), 3.6 (br s, 1H), 3.7 (m, 2H), 4.65 (m, 1H). <sup>13</sup>C NMR (50 MHz): δ 31.18 (q), 44.77 (t), 48.31 (d), 54.23 (d), 56.79 (d), 56.94 (d), 60.79 (d), 83.92 (t), 99.03 (d). IR cm<sup>-1</sup>: 1214, 1067, 1027, 759. Mass: 264, 167, 137, 127, 119, 107, 91, 79.