

# Selectfluor™ F-TEDA-BF<sub>4</sub> mediated and solvent directed iodination of aryl alkyl ketones using elemental iodine†

Stojan Stavber,\* Marjan Jereb and Marko Zupan

Laboratory for Organic and Bioorganic Chemistry, 'Jožef Stefan' Institute and Department of Chemistry, University of Ljubljana, Jamova 39, 1000 Ljubljana, Slovenia. E-mail: stojan.stavber@ijs.si; Fax: +386 1 477 3811

Received (in Cambridge, UK) 7th January 2002, Accepted 28th January 2002

First published as an Advance Article on the web 8th February 2002

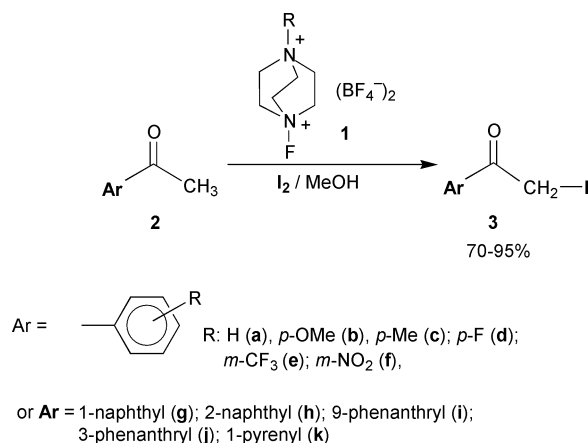
Reactions of aryl alkyl ketones with methanol solution of elemental iodine and 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF<sub>4</sub>) result in the formation of corresponding  $\alpha$ -iodo ketones, while switch over of the regioselectivity can be directed by using acetonitrile as the solvent and selective iodination of the aromatic site of target molecules is thus achieved.

Iodo substituted organic molecules are versatile intermediates in organic synthesis, and above all in carbon-carbon bond formation. In addition, many iodoorganic compounds are biologically active molecules often used in medicine as drugs or diagnostic aids as radioactive labelled markers or contrastors, and therefore their related chemistry has attracted broad interest.<sup>1</sup> Aryl iodides and  $\alpha$ -iodoketones are especially convenient tools for the above mentioned purposes. Direct iodination of an aromatic ring involving electrophilic iodine as the reactive species is the most often used synthetic methodology for the preparation of aryl iodides,<sup>1</sup> and some new reagents or related systems were introduced recently.<sup>2</sup> On the other hand,  $\alpha$ -iodoketones are usually prepared indirectly using halogen interchange reactions or electrophilic iodination of enol acetates and enol silyl ethers, while there has been very little information concerning the direct  $\alpha$ -iodination of ketones.<sup>3</sup> We now report a new method for direct  $\alpha$ -iodination of aryl ketones using elemental iodine as an iodine atom source and the N-F compound, 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**1**), known under the commercial name of Selectfluor™ F-TEDA-BF<sub>4</sub>, as the mediator of the reaction. Organic molecules bearing a reactive N-F bond are excellent reagents for selective fluorination of organic compounds under mild reaction conditions<sup>4</sup> and F-TEDA-BF<sub>4</sub> is one of the most popular members of this family.<sup>5</sup> On the other hand, the N-F reagents possess moderate to strong oxidative power,<sup>6</sup> but investigations taking advantage of this property are still scarce.<sup>7</sup>

In a typical experiment† a mixture of an acetophenone derivative (**2a-f**), iodine and F-TEDA-BF<sub>4</sub>, dissolved in methanol, was stirred at room temperature and after a work-up procedure high to excellent yields of  $\alpha$ -iodocarbonyl substituted products **3a-f** were detected in the crude reaction mixture (Scheme 1). Half of a molar amount of iodine and F-TEDA-BF<sub>4</sub> was established to be sufficient for the conversion of a molar amount of the ketone to its  $\alpha$ -iodo carbonyl derivative. Substituents on the benzene ring had no crucial effect on the course of reaction. The target phenyl methyl ketone molecules bearing a deactivated benzene ring (**2e, 2f**) were also readily transformed to the  $\alpha$ -iodo carbonyl derivatives **3e** and **3f**, but a longer reaction at moderately elevated reaction temperatures (50–60 °C) and an excess of the iodinating reagent (up to 30%) was necessary. Acetyl substituted polynuclear aromatics (**2g-k**) can also be directly transformed to the corresponding iodomethyl aryl ketones **3g-k** in high yield using the mentioned reaction protocol.

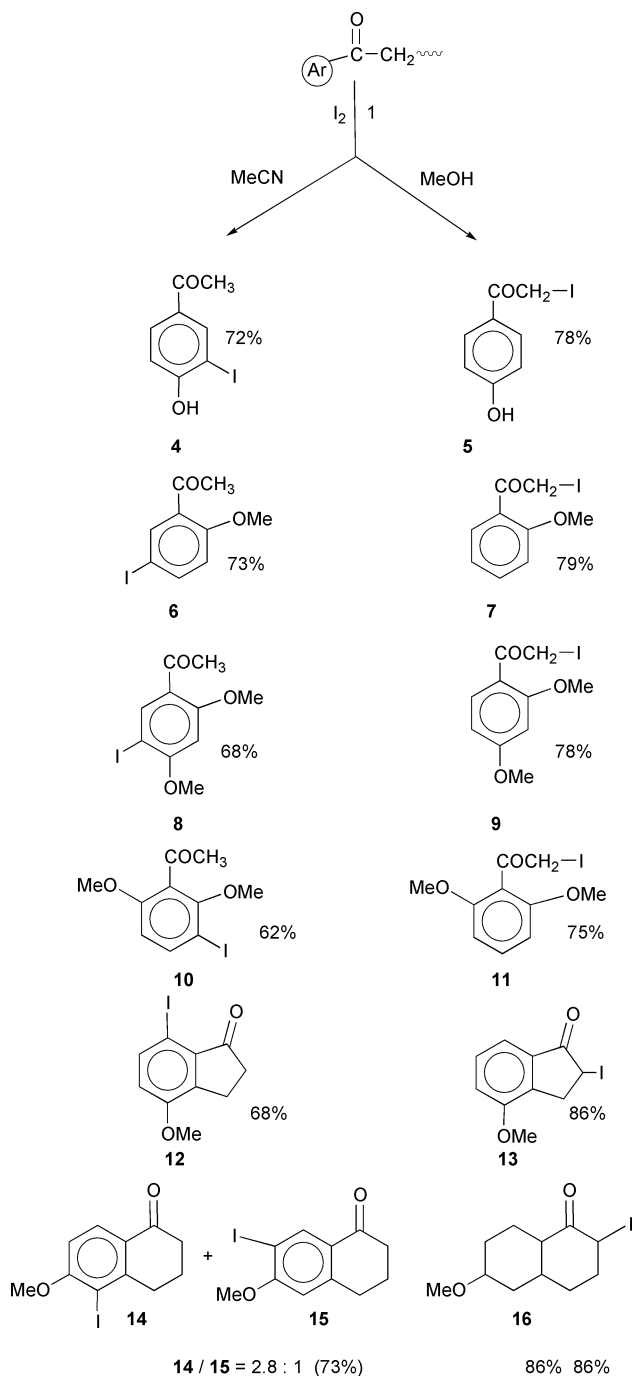
The thus established fact that aryl ketones bearing an activated aromatic part of the molecule could be regioselectively iodinated at the  $\alpha$ -carbonyl position seems at first sight to be in contrast to our earlier observation that *p*-methoxyacetophenone is exclusively iodinated at the phenyl ring using I<sub>2</sub>-F-TEDA-BF<sub>4</sub>, but in that case MeCN was used as solvent.<sup>8</sup> Encouraged by the possibility that the regiochemistry of the iodination process could be regulated merely by the solvent used, we further investigated the reactions of a series of hydroxy and methoxy substituted aryl ketones with the I<sub>2</sub>-F-TEDA-BF<sub>4</sub> system in methanol and in acetonitrile. As follows from the data collected in Scheme 2, the solvent directed regioselectivity of the iodofunctionalisation was confirmed. 4'-Hydroxyacetophenone was regioselectively and almost quantitatively transformed to 3'-iodo-4'-hydroxyacetophenone **4** when the reaction was performed in MeCN, while 1-(4-hydroxyphenyl)-2-iodoethanone **5**, was exclusively formed in MeOH. The same switch of regioselectivity was observed in the case of 2'-methoxy, 2',4'-dimethoxy and 2',6'-dimethoxy substituted acetophenone where ring iodinated products **6, 8**, and **10** were formed in MeCN mediated reactions, while  $\alpha$ -iodocarbonyl derivatives **7, 9, 11** were formed when MeOH was used as solvent. We further confirmed this phenomenon of the switch over of regioselectivity in the case of two methoxy substituted benzocycloalkane-1-one derivatives. The formation of 7-iodo-4-methoxyindan-1-one **12** was established when 4-methoxyindan-1-one was treated with the I<sub>2</sub>-F-TEDA-BF<sub>4</sub> system in MeCN, and 2-iodo-4-methoxyindan-1-one **13** was formed after reaction in MeOH, while a mixture of isomeric aryl iodides **14** and **15** was isolated after MeCN mediated iodination. The  $\alpha$ -iodocarbonyl derivative **16** was regioselectively formed when 6-methoxy-3,4-dihydronaphthalen-1(2H)-one was used as the target molecule and the reaction performed in MeOH.

Concerning the mechanism of this synthetically useful reaction, some preliminary observations should be pointed out. Under the mentioned reaction conditions we did not observe any reaction between elemental iodine and F-TEDA-BF<sub>4</sub>. On the other hand, it is known that F-TEDA-BF<sub>4</sub> is a very effective reagent for the fluorofunctionalisation of activated aromatics as



Scheme 1

† Electronic supplementary information (ESI) available: experimental details. See <http://www.rsc.org/suppdata/cc/b2/b200240j>



Scheme 2

well as of ketones,<sup>4,5</sup> but for these transformations a temperature much higher (60–80 °C) than rt was necessary. Since no significant reaction between aryl methyl ketones **2** and F-TEDA-BF<sub>4</sub> could be observed under the reaction conditions given below, it seems that a three-component reaction system I<sub>2</sub>–F-TEDA-BF<sub>4</sub>–ketone is necessary for the iodination process

and that a rounded-up electron flow, starting from oxidation of I<sub>2</sub> with F-TEDA-BF<sub>4</sub>, and proceeding with attack of the thus formed electrophilic iodine species at the most reactive position on the target aryl alkyl ketone, is the driving force of the reaction. A detailed mechanistic study based on extended experimental data, including kinetic and thermodynamic parameters of the reaction, is in progress and will be published in our forthcoming report.

In conclusion, we can stress the following comparative advantages of the new method for direct and selective iodination of aryl ketones. The reaction protocol is easy to perform and in elemental iodine, as a cost effective source of iodine, both iodine atoms are involved in the iodination process. Further, the method can also be used for aryl ketones bearing a highly activated aromatic ring, while the  $\alpha$ -iodocarbonyl vs. iodoaryl regioselectivity of the reaction can be regulated by the solvent.

The authors are grateful to the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support, and to T. Stipanovic and Professor B. Stanovnik for elemental combustion analysis.

## Notes and references

‡ To a solution of 2 mmol of substituted acetophenone derivative (**2**) in MeCN (20 mL), 254 mg (1 mmol) of elemental iodine and 354 mg (1 mmol) of F-TEDA-BF<sub>4</sub> (**1**) were added and the reaction solution stirred at room temperature until the red colour of the reaction mixture disappeared (1–24 h). The solvent was removed under reduced pressure and the crude reaction mixture dissolved in 50 mL of CH<sub>2</sub>Cl<sub>2</sub>, insoluble material filtered off, the solution washed with aqueous sodium thiosulfate pentahydrate (5%, 20 mL) and water (20 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated, the crude reaction mixtures analysed by <sup>1</sup>H NMR, MS and TLC and amounts of crude products were determined from <sup>1</sup>H NMR spectra of reaction mixture using 1,1-diphenylethane as internal standard while pure products were obtained after flash chromatography over SiO<sub>2</sub> or by preparative TLC. The physico-chemical and spectroscopic characteristics of already known  $\alpha$ -iodoketones were compared with published data, while new compounds were validated as stated in the ESI† and their purity confirmed by elemental analysis.

- 1 E. B. Merkushev, *Synthesis*, 1988, 923; Y. Sasson *Formation of Carbon–Halogen Bonds (Cl, Br, I) in The Chemistry of Functional Groups, Supplement D2: The Chemistry of Halides, Pseudo Halides and Azides, Part 2*, eds. S. Patai and Z. Rappoport, Wiley, Chichester, 1995, 535–620; P. G. Steel *Halobenzenes in Rodd's Chem. Carbon Compd*, 2nd edn., ed. M. Sainsbury, Elsevier, Amsterdam, 1996, 3(1), 178–224.
- 2 A. Bachki, F. Foubelo and M. Yus, *Tetrahedron*, 1994, **50**, 5139; R. D. Chambers, C. J. Skinner, M. Atherton and J. S. Mollet, *Chem. Commun.*, 1995, 19; Y. Noda and M. Kashima, *Tetrahedron Lett.*, 1997, **38**, 6225; T. Muraki, H. Togo and M. Yokoyama, *Synlett*, 1998, 286; S. G. Yang and Y. H. Kim, *Tetrahedron Lett.*, 1999, **40**, 6051.
- 3 T. Okamoto, T. Kakinami, T. Nishimura, I. Hermawan and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1731; J. P. Whang, S. G. Yang and Y. H. Kim, *Chem. Commun.*, 1997, 1355.
- 4 G. S. Lal, G. P. Pez and R. G. Syvret, *Chem. Rev.*, 1996, **96**, 1737; S. D. Taylor, C. C. Kotoris and G. Hum, *Tetrahedron*, 1999, **55**, 12431.
- 5 R. E. Banks, *J. Fluorine Chem.*, 1998, **87**, 1.
- 6 A. G. Gilcinski, G. P. Pez, R. G. Syvret and G. S. Lal, *J. Fluorine Chem.*, 1992, **59**, 157; E. Differding and P. M. Bersier, *Tetrahedron*, 1992, **48**, 1595.
- 7 (a) R. E. Banks, N. J. Lawrence and A. L. Popplewell, *Synlett*, 1994, 831; (b) S. Stavber, P. Kralj and M. Zupan, *Synlett*, 2001, 1152.
- 8 M. Zupan, J. Iskra and S. Stavber, *Tetrahedron Lett.*, 1997, **38**, 6305.