Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2479–2482

Iodine-catalyzed highly efficient Michael reaction of indoles under solvent-free condition

Bimal K. Banik,* Miguel Fernandez† and Clarissa Alvarez†

Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, TX 78541, USA

Received 1 December 2004; revised 7 February 2005; accepted 8 February 2005

Abstract—Michael reaction of indoles with unsaturated ketones has been accomplished in the presence of catalytic amount of iodine under solvent-free condition.

Organic and medicinal chemists are paying tremendous attention for the simplification or improvement of the existing methods that are widely used in the manufacture of pharmaceutical substances. Reactions under solid support, chemoenzymatic reactions and microwave-induced reactions have already created an enormous impact in modern science. Catalytic methods have also contributed significantly. Of particular interest is conducting reactions under solvent-free conditions. These methods proceed with enhanced reaction rates and give cleaner products in many cases.

Michael reaction, a conjugate addition reaction of nucleophiles to unsaturated carbonyl compounds requires basic conditions[1] or acidic catalysts.[2] Many of these methods require stoichiometric amounts of the reagents, and therefore, side reactions can occur if the reactive partners are sensitive.[3] Particularly, polymerization of the unsaturated acceptor is very common because of the acid-induced conditions. Recently, a number of reagents have been developed to overcome the problem. The main improvement of these reagents is the ability to limit the catalysts used.[4]

We have been engaged in the synthesis of several biologically active compounds, including anticancer agents, β-lactams and other heterocyclics.[5] Indoles are well suited for our current program, as several of their derivatives are medicinally active. In connection with our ongoing research to develop iodine-catalyzed organic transformations, we herein report an extremely convenient Michael reaction of indoles using solvent-free conditions.[6]

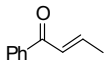
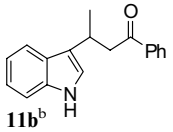
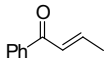
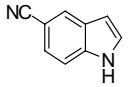
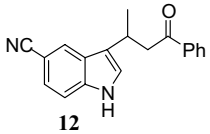
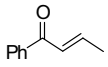
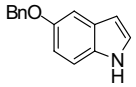
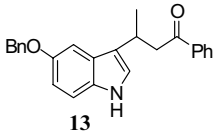
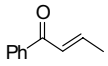
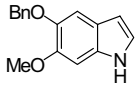
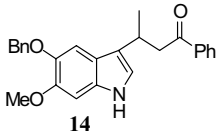
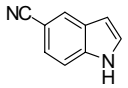
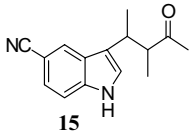
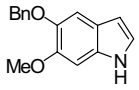
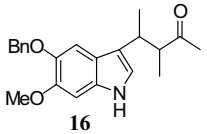
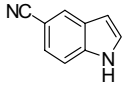
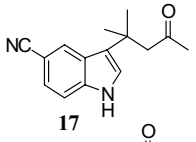
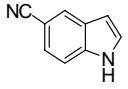
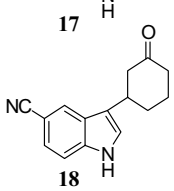
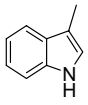
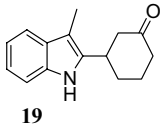
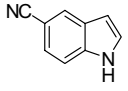
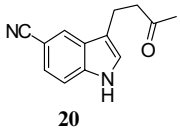
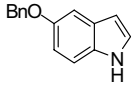
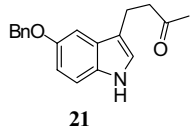
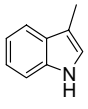
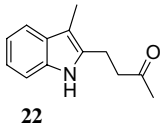
We have reported several iodine-catalyzed organic transformations.[6] For example, protection of carbonyl compounds was achieved as ketals and thioketal by using catalytic quantities of iodine. In another report, a facile oxidation of benzylic alcohols was also investigated. In addition, iodine-catalyzed glycosylation of alcohols with sugar derivatives is also known. These are acid-induced processes. As Michael reactions are among the most important acid-mediated reactions, development of a reaction that uses catalytic quantities of lowly toxic, readily available, economic reagent without using any solvent should greatly contribute to the creation of environmentally benign processes. Since, most of the common acceptors used in this type of reaction are liquids, we hypothesized that the drawbacks of the catalysts employed in the Michael reaction may be avoided if we used iodine as a mild reagent in catalytic amounts under solvent-free conditions.

Several addition reactions of enones to indoles using Lewis and Bronsted acids have been published.[7] Acid-induced reaction of indoles requires precise control of the acidity to prevent side reactions, including dimerization and polymerization.[8] Recently, it has been demonstrated that indium tribromide mediates the conjugate addition of enones to indoles.[9] However, with less electron-rich indoles, the yield of the products was not satisfactory. In such cases, indium trichloride was proved to be very effective. However, these reactions were done under classical conditions using organic

* Corresponding author. Tel.: +1 956 380 8741; fax: +1 956 384 5006; e-mail: banik@panam.edu
† Undergraduate research participants; contributed equally.

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.02.044

Table 1. I_2-catalyzed Michael reaction of enones with indoles[a]

Entries	Enones	Indoles	Products	Yield (%)
1			 **11b**[b]	85
2			 **12**	78
3			 **13**	72
4			 **14**	69
5			 **15**	56
6			 **16**	73
7			 **17**	64
8			 **18**	79
9			 **19**	55
10			 **20**	76
11			 **21**	71
12			 **22**	45

[a] Reaction was completed within 20 min at room temperature.

solvent and approximately 10 mol % of the catalyst for 16–24 h. In addition, in some cases, external proton source such as isopropyl alcohol was needed for the success of the reaction.

Our method of iodine-catalyzed Michael reaction of indoles with enones is very simple and efficient (Table 1). The starting materials (indoles and ketones, 1:1, 1 mmol scale) are mixed with iodine (1 mol %) and the mixtures are stirred. After the specified time (10–20 min) at room temperature, dichloromethane (25 mL) is added to bring the mass in solution. It is then washed with sodium thiosulfate and the solvent is evaporated under reduced pressure. The crude material in most of the cases is sufficiently pure (80–90%). The pure products are obtained by a simple filtration through silica gel using ethyl acetate–hexanes (20:80). Unlike the processes described in earlier reports, this method is totally independent of solvent choice[10] or external proton source.[9a] Even reagents that are undistilled or unpurified can be used with equal success. Additionally, it has been found that the indoles with wide range of functionalities react very easily with cyclic and acyclic enones and give products in high yield at room temperature in the presence of only 1 mol % iodine as the catalyst. Specifically, the reactions are very efficient, and the products are not contaminated with side products, such as dimers or trimers which are normally formed under the influence of strong acids.[9b] In general, the reactions took place at the 3-position of the indole ring when this position was unoccupied. When the 3-position was occupied by a methyl group, the reaction took place at C_2 positions.

To expand the method, reaction of imidazole with 3-methylcyclohex-2-ene and methyl vinyl ketone was performed in the presence of iodine (5 mol %). The yield of the products was 60–70%. However, the reaction was not successful with unsaturated ester and unsaturated aldehyde.

The success of iodine-mediated conjugate reactions prompted us to investigate the mechanistic process. Catalytic amounts (1 mol %) of iodine crystal is necessary for a complete reaction, an increase in the proportion to 10% produced comparable yields. The reaction did not proceed in the absence of iodine. Since this reaction is investigated without using inert atmosphere and dry conditions, iodine can produce hydroiodic acids. Therefore, a reaction (Table 1, entry 1) was performed in the presence of hydroiodic acid in various amounts under solvent-free conditions. It appeared that hydroiodic acid-mediated reactions produced products in much lower yields (10%). Most of the experiments under hydroiodic acid-induced processes remained incomplete even after 5 h. With catalytic amounts of hydroiodic acid, reaction did not proceed at all. This result suggests that there might be a complexation role for molecular iodine apart from its acidity.

In conclusion, Michael reaction of indoles and imidazoles with unsaturated carbonyl compounds was successfully carried out in the presence of a catalytic amount of iodine in the absence of solvent.[11] In contrast to the existing methods, this procedure is simple, rapid, high-yielding, and convenient.

Acknowledgements

We gratefully acknowledge the partial financial support for this research from The Robert A. Welch Foundation (BG-0017) departmental grant and The University of Texas-Pan American.

References and notes

1. (a) Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett* **2000**, 1257; (b) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700.
2. Rosenthal, D.; Braundrup, G.; Davis, K. H.; Wall, M. E. *J. Org. Chem.* **1965**, *30*, 3689.
3. (a) Clariana, J.; Galvez, N.; Marchi, C.; Moreno-Manas, M.; Vallribera, A.; Mollins, E. *Tetrahedron* **1999**, *55*, 7331; (b) Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259; (c) Giuseppone, N.; Vander Weghe, P.; Mellah, M.; Collin, J. *Tetrahedron* **1998**, *54*, 13129.
4. (a) Cabral, J.; Laszlo, P.; Mahe, L.; Montaufier, M.-T.; Randriamahefa, S. L. *Tetrahedron Lett.* **1989**, *30*, 3969; (b) Perez, M.; Pleixats, R. *Tetrahedron* **1995**, *51*, 8355; (c) Falborg, L.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823; (d) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615; (e) Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *2*, 3393; (f) Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. *Chem. Commun.* **2001**, *2*, 1240; For a review for enantioselective conjugate addition, see: Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.
5. (a) Becker, F. F.; Banik, B. K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2877; (b) Becker, F. F.; Mukhopadhyay, C.; Hackfeld, L.; Banik, I.; Banik, B. K. *Bioorg. Med. Chem.* **2000**, *8*, 2693; (c) Banik, B. K.; Becker, F. F. *Bioorg. Med. Chem.* **2001**, *9*, 593; (d) Banik, B. K.; Becker, F. F. *Curr. Med. Chem.* **2001**, *8*, 1513; (e) Banik, I.; Becker, F. F.; Banik, B. K. *J. Med. Chem.* **2003**, *1*, 12; (f) Banik, B. K.; Becker, F. F.; Banik, I. *Bioorg. Med. Chem.* **2004**, *12*, 2523.
6. (a) Mukhopadhyay, C.; Becker, F. F.; Banik, B. K. *J. Chem. Res.* **2001**, 108; (b) Samajdar, S.; Basu, M. K.; Becker, F. F. *Synlett* **2002**, 319; (c) Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2001**, *42*, 4425; (d) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213; For other iodine-catalyzed organic reactions, see: (a) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1994**, *59*, 4714; (b) Banik, B. K.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1997**, *38*, 5077; (c) Banik, B. K.; Zegrocka, O.; Manhas, M. S.; Bose, A. K. *Heterocycles* **1997**, *46*, 173.
7. (a) Harrington, P. E.; Kerr, M. A. *Can. J. Chem.* **1998**, *76*, 1256; (b) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047; (c) Iqbal, Z.; Jackson, A. H.; Rao, K. R. N. *Tetrahedron Lett.* **1988**, *29*, 2577; (d) Szmuszkovicz, J. *J. Am. Chem. Soc.* **1957**, *79*, 2819.
8. (a) Houlihan, W. J. In *Indoles*; John Wiley & Sons: New York, 1972; Vol. 1, p 71; (b) Iqbal, Z.; Jackson, A. H.; Rao, K. R. *Tetrahedron Lett.* **1988**, *29*, 21.
9. (a) Bandini, M.; Cozzi, P. G.; Giacomoni, M.; Melchiorre, P.; Selva, S.; Ronchi, A. U. *J. Org. Chem.* **2002**, *67*, 3700; (b) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165.

10. Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319.
11. A representative procedure is given below: Iodine (5 mol %) was added to a mixture of indole (1 mmol) and ketone (1 mmol). After being stirred for 30 min, the mixture was chromatographed over silica gel using ethylacetate–hexane (10:90) to afford the pure product.