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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 5345–5349

Molecular iodine in isopropenyl acetate (IPA): a highly efficient catalyst for the acetylation of alcohols, amines and phenols under solvent free conditions

Naseem Ahmed and Johan E. van Lier*

Department of Nuclear Medicine and Radiobiology, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, Québec, Canada J1H 5N4

Received 2 May 2006; revised 16 May 2006; accepted 17 May 2006
Available online 12 June 2006

Abstract—Iodine in isopropenyl acetate (IPA) is a highly efficient catalyst for the acetylation of a variety of alcohols, phenols and amines under solvent free conditions. Primary, secondary, tertiary alcohols, amines and mono to polyhydroxy phenols and anilines with electron donating or withdrawing substituents can be easily acetylated in good to excellent yield at 85–90 °C.

The acetylation of alcohols, phenols, amines and anilines is an important and widely used transformation in organic synthesis and a number of reagents coupled with promoters or catalysts have been put forth. Among them, acid halides (acetyl chloride) and acid anhydrides are usually employed as the acetylating agents in the presence of an acid or base catalysts.[1] The various catalysts that have been developed for acetylation include Et_3N,[2a] pyridine[2a] or DMAP,[2b] *t*-Bu_3P that was subsequently introduced for base sensitive compounds,[2c] metal salts such as $CoCl_2$,[3] $TaCl_5$–SiO_2,[4] $ZnCl_2$,[5a] ZnO,[5b,c] $InCl_3$,[6a] $ZrCl_4$,[6b] $LiClO_4$,[6c] Ru-catalysts,[6d] $Mg(ClO_4)_2$,[6e] SmI_2,[6f] $CeCl_3$,[6g] $ZrOCl_2{\cdot}8H_2O$,[6h] montmorillonite,[7] zeolite-microwave,[8] different triflates,[9] I_2,[10] PTSA,[11a] NH_2SO_3H,[11b] distannoxane,[11c] ionic liqiuds,[11d] solid supported reagents and lipase enzymes.[11e]

Previously we have used isopropenyl acetate (IPA, or 2-propenyl acetate) in the presence of H_2SO_4 and PTSA for enol acetate formation and the protection of phenolic alcohols in steroids syntheses.[12] IPA is also used as an alternative innocuous acyl donor to acid halides and acid anhydride in acetylation reactions of alcohols, amines and phenols.[10a] This process is activated by addition of a catalytic amount of protic or Lewis acid such as H_2SO_4,[13a] PTSA,[13b] Shvo's catalyst,[13c] distannoxane catalyst[13d] and lipase enzymes.[13e] Most of the above procedures can be applied to the acylation of various acid/base sensitive substrates. However, limitations in terms of reagent availability, prolonged reaction times, formation of unwanted side products, need for halogenated solvents and excess acetylating reagent remain. Hence, there is a need for improved reagents for the acetylation of selected substrates. Acetylation of alcohol, amine and phenol functional groups is of particular importance during synthetic sequences in the preparation of steroids, carbohydrates, nucleosides and other natural products. Also, acetylated products are important intermediates for the Fries rearrangement, which produces useful ketones.[14]

In recent years, iodine has been used as a Lewis acid catalyst for many organic transformations,[15] including the acetylation of alcohols and phenols with acid anhydride as a powerful catalyst.[15a] However, under solvent free conditions this reaction only proceeds rapidly in the presence of liquid substrates. In the case of solid substrates, dichloromethane is used as a solvent, which results in low yields, even after extended reaction times of 72 h. Here we describe a highly efficient and convenient procedure for the acetylation of both solid and liquid alcohols, amines and phenols under solvent free conditions in the presence of IPA and a catalytic amount of iodine at 85–90 °C (Scheme 1). To our knowledge, studies exploiting this catalyst for such conversions have not previously been reported.

Keywords: Iodine; Lewis acid; Isopropenyl acetate (IPA); Acetylation; Alcohols; Amines.
* Corresponding author. Tel.: +1 819 564 5409; fax: +1 819 564 5442; e-mail: johan.e.vanlier@USherbrooke.ca

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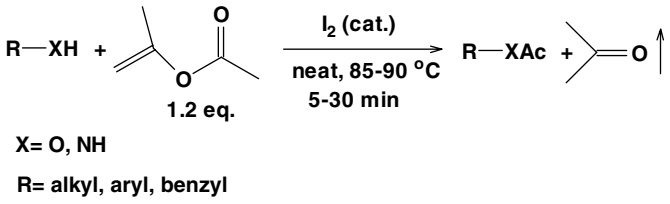
doi:10.1016/j.tetlet.2006.05.122



Scheme 1.

Table 1. IPA acetylation catalyzed by molecular iodine

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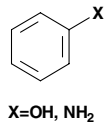
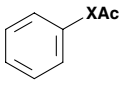
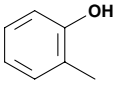
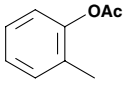
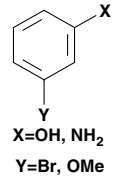
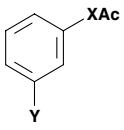
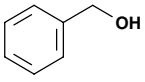
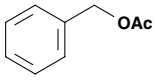
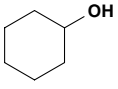
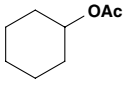
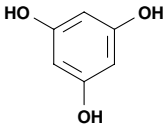
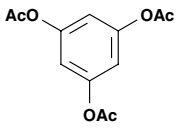
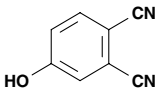
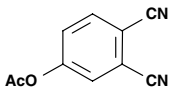
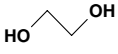
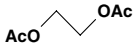
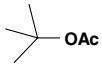
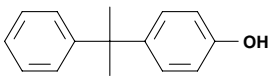
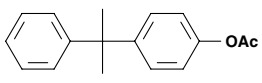
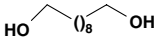
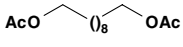
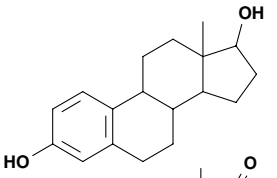
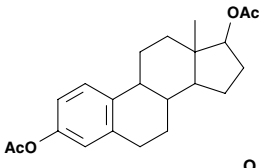
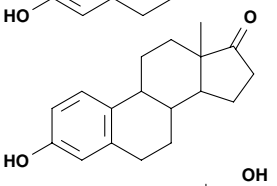
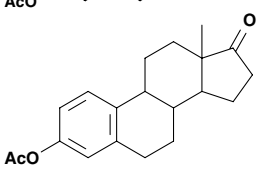
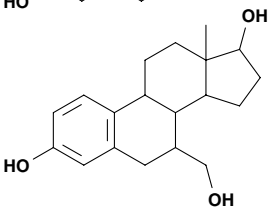
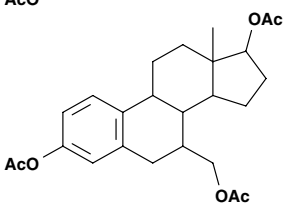
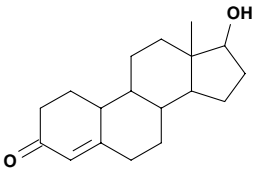
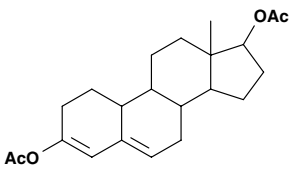
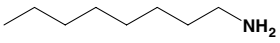
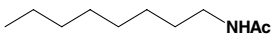
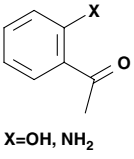
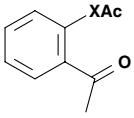
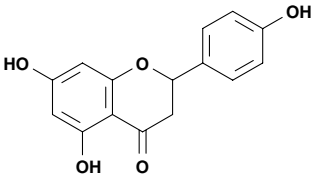
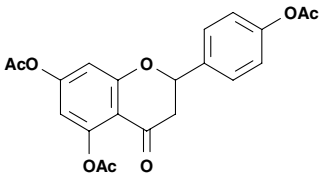
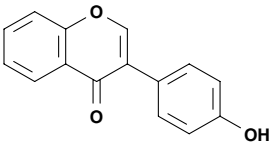
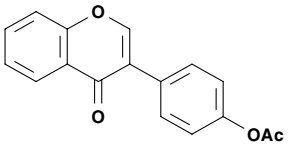
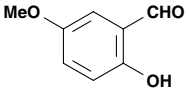
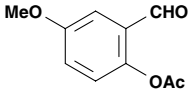
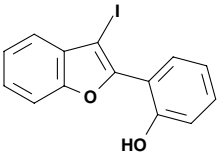
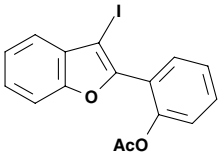
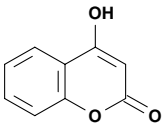
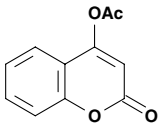
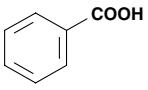
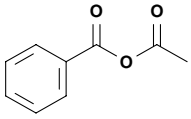
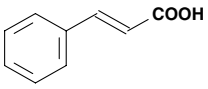
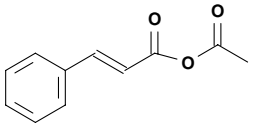
1	 X=OH, NH_2		99 (5)
2			99 (5)
3	 X=OH, NH_2 Y=Br, OMe		98 (10)
4			98 (5)
5			97 (5)
6			97 (45)[c]
7			98 (10)
8			91 (10)
9			75 (5)
10			97 (5)
11			92 (20)

Table 1 (*continued*)

Entry	Substrate	Product[c]	Yield,[a,b] % (Reaction time, min)
12			95 (10)
13			96 (5)
14			90 (25)
15			91 (15)[d]
16			86 (15)
17			87 (20)
18			85 (35)
19			90 (10)
20			70 (15)
21			92 (10)

(*continued on next page*)

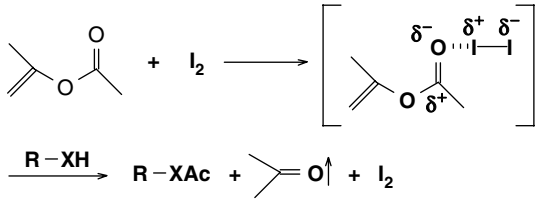
Table 1 (*continued*)

Entry	Substrate	Product[c]	Yield,[a,b] % (Reaction time, min)
22			95 (10)
23			65 (25)[e]
24			60 (30)[e]

[a] Substrate (1.0 mmol) and IPA (0.15 ml) were stirred at 85–90 °C, followed by the addition of I_2 (5–10 mg, 0.02–0.04 mmol) and continuous stirring for the indicated reaction time.
[b] Isolated and non-optimized yield.
[c] Identification of the products was ascertained by ^1H and ^{13}C NMR, mass spectroscopy and comparison with available lit. data.
[d] The ketone at position 3 was also acetylated in excellent yield.
[e] The spectral data of the products were identical to those reported in Ref. 17.

Using a simple experimental procedure,[16] a wide range of substituted acetylation products were obtained from their corresponding alcohols, amines and phenols within 5–45 min at 85–90 °C in high yields (Table 1). The assigned structures were established from their spectral properties (IR, ^1H and ^{13}C NMR, and MS) and by comparison with available authentic data. In the absence of iodine, using the same reaction conditions, products were obtained in low yield (30–40%), even after prolonged reaction times of 1.5 h. The general applicability and efficiency of this reaction is evident from the wide range of mono- through poly-hydroxyl compounds, amines, anilines and phenols that react in excellent yields in a short reaction time (Table 1). Overall the procedure works well with a 1:1.2 molar ratio of substrate to IPA in the presence of a catalytic amount of iodine (0.2–0.4 mol) without solvent, at 85–90 °C. In the case of poly-hydroxyl compounds (e.g., entry 6) 1.5–2.5 equiv of IPA gave better results; the presence of functional groups such as halogens, aldehyde, ketone and double bonds were tolerable. However, substrates containing triple bonds decomposed at this temperature; continuous stirring at room temperature for 24 h gave the product in poor yield. In the case of entry 15, the ketone group was also acetylated at the indicated temperature. Furthermore, using carboxylic acids as substrates (entries 23 and 24) also resulted in mixed anhydride formation in good yields (Table 1).

During the reaction with partially insoluble substrates in IPA at 85–90 °C, we observed that the material readily dissolved upon addition of the iodine catalyst. It thus appears that the iodine functions as a practical promoter of the acetylation reactions by polarizing IPA, releasing acetone (i.e., a good solvent), which subsequently evaporates from the reaction mixture during the heating process (Scheme 2).



Scheme 2. Proposed iodine-promoted acetylation reaction.

In conclusion, we have shown that molecular iodine in isopropenyl acetate has strong Lewis acid catalytic properties facilitating the acetylation of alcohols, amines and phenols, and the mixed anhydride formation of carboxylic acids under solvent free condition. The advantages of this procedure over earlier reported processes includes its simplicity, fast and clean reactions, high yield, and the absence of organic solvent. After submitting this manuscript, a related study on the catalytic activity of molecular iodine for the acetylation of alcohols with vinyl acetate appeared in this journal.[18]

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (CIHR, Grant MOP- 44065).

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16. *General procedure for acetylation*: To a stirred mixture of alcohols, amines, phenols or acid (1 mmol) and isopropenyl acetate (IPA, 0.15 ml, 1.2 equiv) at 85–90 °C was added iodine (5–10 mg, 0.02–0.04 mmol) with continued stirring at the same temperature for the indicated time. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and the remaining iodine was destroyed by adding 5% aq solution of sodium thiosulfate (2 ml). Diethyl ether (5–10 ml) was added and the phases were separated. The organic phase was washed with a saturated solution of $NaHCO_3$ (5 ml), dried over anhyd Na_2SO_4 and concentrated under vacuo. If necessary the product was purified by column chromatography on silica gel in hexane/ethyl acetate. All products were characterized by comparison of their spectral and physical properties with those of authentic samples.
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