GREEN SYNTHESIS OF BENZAMIDES IN SOLVENT- AND ACTIVATION-FREE CONDITIONS

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GRAPHICAL ABSTRACT

Abstract Herein, we describe a clean and ecocompatible pathway for both N-benzoylation and N-acetylation of anilines, amines, diamines, and aminoalcohols using three enol esters with good yields. We have improved the use of vinyl benzoate for the direct introduction of a benzamido-moiety under solvent- and activation-free conditions. The recovered amides are easily isolated by crystallization.

Keywords Acetylation; anilines; benzoylation; enol esters; green chemistry

INTRODUCTION

The development of new methodologies for the synthesis of bioactive molecules is growing rapidly.1 The amide bond is found in many key building blocks involved in the synthesis of a variety of molecules2 for therapeutic, cosmetic,
and food-processing uses. In organic synthesis, the creation of an amide bond is a necessary step to protect a primary amine in mono-, bi-, or/and poly-functional molecules. The acetamido- or benzamido-moieties are especially important for protecting free amino-groups. In fact, the study of N- and O-acetylation of amines, alcohols, amino acids, and amino alcohols is still drawing the attention of chemists and the development of new ecocompatible ways to synthesize amides remains challenging. Compared to the N-benzylation, the N-acetylation of amines has been well studied. It is usually performed using acetyl chloride, anhydrides, carboxylic acids, or esters. However, the first one is routinely realized with benzoyl chloride despite its greater toxicity and requires a base such as pyridine, triethylamine, or sodium hydroxide as catalyst.

The literature shows that in order to perform the acetylation of amines, activation such as heating, microwave irradiation, or a catalyst is required. Although being environmentally friendly, enol esters as acetyl donors are scarcely described as amidation agents. Enol esters are largely used in enzymatic transesterification, allowing the kinetic resolution of racemic benzylic alcohols. The first catalyst- and base-free synthesis of amides using enol amino esters was described in 1991 by Kabouche et al. This seminal work was later developed by Chen et al., who described the selective acetylation of amines and diols using vinyl carboxylates as leaving groups. Ahmed and Lier synthesized acetanilides with good yields by employing isopropenyl acetate at 85 to 90°C with iodine as catalyst. The acetylation of primary amines with vinyl acetate under microwave irradiation has been described by Ferroud et al. More recently, Pelagalli et al. disclosed that the acetylation of primary and secondary amines with isopropenyl acetate can be realized without solvent, although heating at 60°C was required to achieve the desired reaction.

The protection of aromatic amines, especially anilines, is very important for the production of colorants, pesticides, herbicides, and drugs, although difficult to perform. This work describes the new synthesis of benzamides by vinyl benzoates and N-acetylation of amines, especially the aromatic one using enol esters as acyl donors. Three enol esters are compared and the scope of this reaction has been extended to aliphatic, cyclic, aromatic and benzylic primary amines, diamines, and amino alcohols.

**ACETAMIDE SYNTHESIS**

First, to determine the optimal conditions, we have studied the N-acetylation of benzylic, aliphatic, and aromatic primary amines (1–4) by vinyl acetate (VA) and isopropenyl acetate (IA) (Scheme 1). These amines have been selected for their potential industrial and therapeutic interest. The reaction was performed with 1 mmol of amine and 1 to 3 equivalents of the acetylating agent, without solvent, and under magnetic stirring. The reaction was monitored by thin-layer chromatography (TLC).

After complete consumption of the starting amine the excess of the acetylating agent was removed by evaporation and the crude reaction mixture was analyzed by 1H NMR. This analysis shows complete conversion of the starting material and quantitative formation of a single amide for each substrate depicted in Table 1. The desired amides were isolated as pure products after purification as shown by 1H and 13C NMR analysis. The results are presented in Table 1.
Table 1. Acetylation of various amines with vinyl acetate and isopropenyl acetate

| Entry | Substrate\(^a\)/product | AA | Amount of AA (mmol) | Time (h)\(^b\) | Yield (%)*
|-------|------------------------|----|---------------------|----------------|------------
| 1     |                       | VA | 3                   | 2              | 85         |
| 2     |                       |    | 1                   | 4              | 61         |
| 3     |                       | IA | 3                   | 3              | 92         |
| 4     |                       |    | 2                   | 12             | 92         |
| 5     |                       |    | 1                   | 21             | 87         |
| 6     |                       | VA | 3                   | 1              | 89         |
| 7     |                       |    | 1                   | 21             | 75         |
| 8     |                       | IA | 3                   | 2              | 90         |
| 9     |                       |    | 2                   | 5              | 89         |
| 10    |                       |    | 1                   | 5              | 83         |
| 11    |                       | VA | 3                   | 2              | 70         |
| 12    |                       |    | 1                   | 3              | 72         |
| 13    |                       | IA | 3                   | 1 min          | 86         |
| 14    |                       |    | 2                   | 1              | 85         |
| 15    |                       |    | 1                   | 1              | 62         |
| 16    |                       | VA | 3                   | 24             | 70         |
| 17    |                       |    | 1                   | 48             | 61         |
| 18    |                       | IA | 3                   | 24             | 69         |
| 19    |                       |    | 2                   | 24             | 59         |
| 20    |                       |    | 1                   | 48             | 57         |

\(^a\)1 mmol of amine, the appropriate amount of enol ester, without solvent, under magnetic stirring at room temperature.

\(^b\)After total conversion.

*Isolated yields of pure acetamides after purification by simple workup or by crystallization.

Scheme 1. Acetamide synthesis.
The concentration of the acetyl donor has a significant effect on the \( N \)-acetylation of primary amines (1–4). Increasing the amount of the acetylating agent from 1 to 3 equivalents decreases the reaction time and improves the isolated yields of the amides (1–4). Indeed, only 1 equivalent of the acetyl donor led to a slower reaction. However, using 3 equivalents led to a much faster reaction (3 h vs. 21 h, entries 3 and 5; 1 min vs. 1 h, entries 13 and 15). As can be seen in Table 1, the results strongly depend on the nature of the amine. Using aliphatic amines 2 and 3 led to short reaction times whatever acetylating agent was employed (entries 6–15). With benzylic amine 1 reaction times of 2 h using VA and 3 h using IA were observed. The reaction was much slower using aromatic amine 4 (entries 16–20). We were pleased to find that the analgesic acetanilide 4a has been obtained within 70% yield (entry 16) under milder conditions than previously described, without heating and in absence of catalyst.[13]

It was thus found that isopropenyl acetate afforded much shorter reaction times than vinyl acetate and allows isolation of the acetamides in good yields. Therefore, isopropenyl acetate can be considered as a better acetyl donor than vinyl acetate. The best results were obtained using 3 mmol of IA. It can be easily removed from the reaction mixture and no secondary reaction has been observed. The whole process seems competitive for the preparation of amides.

**SCOPE OF THE AMIDATION OF PRIMARY AMINES USING IA**

The scope of the reaction was determined using various primary amines. Aromatic, benzylic, cyclic, and heterocyclic amines and amino alcohol were employed (5–23) to study electronic or steric effects (Scheme 2). The reactions were performed under the optimal conditions previously determined, with (1:3) amine/isopropenyl acetate ratio and at room temperature.

All the amides were obtained after evaporation of residual IA and acetone by-product. The results are presented in Table 2. The structures of all products were determined by \(^1\)H and \(^13\)C NMR analyses.

The results mentioned in Tables 1 and 2 show that isopropenyl acetate is an efficient acetyl donor toward the \( N \)-amidation of most amines. Benzylic amines were obtained quantitatively (Table 1, entry 3; Table 2, entries 1–9) within 3 h or less. Increase of the acetylation time rate of amine 6 compared to 5 is due to the presence of two activating methoxy groups (Table 2, entries 1 and 2). Total conversions of aliphatic and benzylic amines were observed and the acetamides were isolated in good yields. The reaction times depend on the structure of the amine. While the acetamide 3a was obtained instantaneously (Table 1, entry 13), the acetamide 2a
Table 2. Acetylation of primary amines by isopropenyl acetate

| Entry | Substrate/product | Time (h) | Yield (%) |
|-------|-------------------|----------|-----------|
| 1     | ![Structure](5)   | 3        | 100       |
| 2     | ![Structure](6)   | 20 min   | 100       |
| 3     | ![Structure](7)   | 2        | 100       |
| 4     | ![Structure](8)   | 2        | 100       |
| 5     | ![Structure](9)   | 1.5      | 100       |
| 6     | ![Structure](10)  | 3        | 85        |
| 7     | ![Structure](11)  | 3        | 70        |
| 8     | ![Structure](12)  | 3        | 100       |
| 9     | ![Structure](13)  | 2        | 100       |

(Continued)
| Entry | Substrate<sup>a</sup>/product | Time (h)<sup>b</sup> | Yield<sup>c</sup> (%) |
|-------|-------------------------------|---------------------|---------------------|
| 10    | ![Substrate 14](image1) ![Product 14a](image2) | 3                   | 100                 |
| 11    | ![Substrate 15](image3) ![Product 15a](image4) | 24                  | 94                  |
| 12    | ![Substrate 16](image5) ![Product 16a](image6) | 24                  | 73                  |
| 13    | ![Substrate 17](image7) ![Product 17a](image8) | 96                  | 28                  |
| 14    | ![Substrate 18](image9) ![Product 18a](image10) | 3                   | 90                  |
| 15    | ![Substrate 19](image11) ![Product 19a](image12) | NR                  |                     |
| 16    | ![Substrate 20](image13) ![Product 20a](image14) | 24                  | 100                 |
| 17    | ![Substrate 21](image15) ![Product 21a](image16) | 24                  | 60                  |

(Continued)
was formed within 2 h (Table 1, entry 8) and the cyclic acetamide 15a within 24 h (Table 2, entry 11).

Aromatic amides were obtained in good yields under the same conditions in some cases. Both reaction time and isolated yields were influenced by the substitutions on the aromatic ring. Aniline 4 (Table 1, entry 18) and para-toluidine 16 (Table 2, entry 12) were acetylated within 24 h in 69% and 73% yields respectively. The presence of \(-\text{CF}_3\) group led to a decrease in yield of 17a and an increase in reaction time (4 days, Table 2, entry 13). On the other hand, the presence of an acetyl substituent in meta-position the aromatic ring (Table 2, entry 14) afforded the corresponding acetamide 18a in good yield. Furthermore, the aminothiophene 10 and aminofuran 11 have been acylated in 3 h and corresponding amides were obtained in 70% and 85% yields respectively (entries 6 and 7). The acetylation of aminopyridine 19 did not proceed (entry 15). We have also tried the acetylation of an alkylaminopyridines without any results.

The study of N-acetylation was extended to bifunctional molecules of therapeutic interest and studied under the conditions determined previously. The primary amine function of amino alcohols 20 and 21 was selectively N-acetylated (entries 16 and 17). The isolated yields depend on the steric effects. The substrate 22 substituted by morpholine group is protected quantitatively within 40 min (entry 18). While the bulky substrate 23 with a furoyl substituent possessing secondary amine moiety was N-acetylated (entry 19) and amide 23a was obtained quantitatively in short time.

### BENZAMIDES SYNTHESIS USING VINYL BENZOATE (VB)

Because N-benzylation is an important reaction in organic synthesis, it was decided to study the protection of whole substrates (1–25) with vinyl benzoate (VB) under conditions previously determined (Scheme 3). The reaction was performed using 3 equivalents of the benzyolating agent and monitored by thin-layer
chromatography (TLC). After consumption of the starting amine, the corresponding benzamides were isolated by crystallization or by flash chromatography. The results are summarized in Table 3.

**Scheme 3.** Benzoylation of primary amines.

**Table 3. Benzamide synthesis using vinyl benzoate**

| Entry | Substrate<sup>a</sup>/benzamide | Time (h)<sup>b</sup> | Yield<sup>c</sup> (%) |
|-------|------------------|-----------------|-----------------|
| 1     | 2
| 2     | 3b              | 3               | 87              |
| 3     | 1b              | 24              | 82              |
| 4     | 5b              | 24              | 70              |
| 5     | 6b              | 24              | 68              |
| 6     | 7b              | 24              | 55              |

(Continued)
| Entry | Substrate<sup>a</sup>/benzamide | Time (h)<sup>b</sup> | Yield<sup>c</sup> (%) |
|-------|---------------------------------|---------------------|-------------------|
| 7     | ![Chemical Structure 7](image)    | 24                  | 60                |
| 8     | ![Chemical Structure 8](image)   | 24                  | 94                |
| 9     | ![Chemical Structure 9](image)   | 24                  | 48                |
| 10    | ![Chemical Structure 10](image)  | 24                  | 50                |
| 11    | ![Chemical Structure 11](image)  | 24                  | 69                |
| 12    | ![Chemical Structure 12](image)  | 24                  | 69                |
| 13    | ![Chemical Structure 13](image)  | 24                  | 55                |

(Continued)
As shown in Table 3, vinyl benzoate acts as an efficient benzoylating agent. Reaction times were varied from 40 min to 48 h. Isolated yields from 48% to 100%, depending on the steric and the electronic properties of amines, were
obtained. Most of the substrates reacted smoothly (entries 1–12), whereas aromatic amines, especially anilines 4, 16, 17, and 18 did not react to form the desired benzamides. It was unexpected, considering that the acetylation of such amines was possible by using IA (Table 1, entry 18; and Table 2, entries 12–14). On the other hand, the heterocyclic substrates such as the alkylaminopyridines 24 and 25 afforded the corresponding benzamides 24b and 25b with 90% and 73% yields, respectively (entries 18 and 19), while their acetylation could not be realized. These reversed reactivities compared to the acetylation might be explained by the bulkiness and the electronic effects of both the benzoylating agent and the amines. The amino alcohols 20 and 21 were selectively N-benzoylated (entries 15 and 16). Vinyl benzoate afforded the desired products in lower yields and longer reaction times than isopropenyl acetate. It might be explained by steric effects, because vinyl benzoate is more hindered than IA.

CONCLUSION

In summary, to perform the protection of several primary amines, anilines, and bifunctional molecules, three enol esters were compared. Vinyl acetate, isopropenyl acetate, and vinyl benzoate were employed to synthesize various amides. Both the N-benzoylations and the N-acetylations were performed with satisfactory isolated yields and reaction times. Soft reaction conditions were employed, at room temperature, without solvent and without any catalyst. The direct introduction of a benzamido-moiety realized under solvent-free conditions and without activation is especially important for protecting amino groups. The difference of reactivity among BV, VA, and IA showed their complementarity, allowing the protection of a large broad of amines and of some bifunctional molecules. This methodology respects the principles of green chemistry and can therefore be applied toward the clean synthesis of polyfunctional molecules.

EXPERIMENTAL

All starting materials and reagents used in this study were obtained commercially from Aldrich and Acros and were used without purification. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica-gel plates (60F-254) using ultraviolet light (254 nm) as the visualizing agent and ninhydrine solution and heat as developing agents. NMR spectra were recorded on Brucker spectrometers (300 MHz for $^1$H, 75 MHz for $^{13}$C). Chemical shifts are reported in δ ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard for $^1$H NMR and chloroform-d ($\delta$ 77.0 ppm) for $^{13}$C NMR. Coupling constants ($J$) are given in hertz. The following abbreviations classify the multiplicity: s, singulet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad signal.

Preparation of the Acetamides

In a round-bottomed flask, a mixture of a suitable amine (1 eq.) and the appropriate enol ester (isopropenyl acetate or vinyl acetate) (3 eq.) was stirred at room temperature for the indicated time. The evolution of the reaction was monitored.
by TLC. After complete consumption of the amine, the crude reaction mixture was concentrated in vacuo and the amide was directly obtained pure. If it was not the case, a simple acidic workup was required to purify the obtained acetamide.

**Preparation of the Benzamides**

In a round-bottomed flask, a mixture of a suitable amine (1 eq.) and 3 eq. of vinyl benzoate were stirred at room temperature for 24 h. The evolution of the reaction was monitored by TLC. After complete consumption of the amine, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel (CH₂Cl₂ as eluent) or by crystallization using hexane as the crystallization solvent to gave the pure benzamides.

**ACKNOWLEDGMENT**

We thank M. Loïc Cornelissen for his contribution for the preparation of this article.

**FUNDING**

MESRS (FNR 2000 and PNR) and FNRS are gratefully acknowledged for financial support of this work.

**SUPPORTING INFORMATION**

All experimental details, NMR characterization, and spectra can be accessed on the publisher’s website.

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