

ORGANOCATALYTIC SYNTHESIS OF AMIDES FROM ALDEHYDES THROUGH *p*-NITRO PHENOL ESTER ACTIVATION

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ABSTRACT

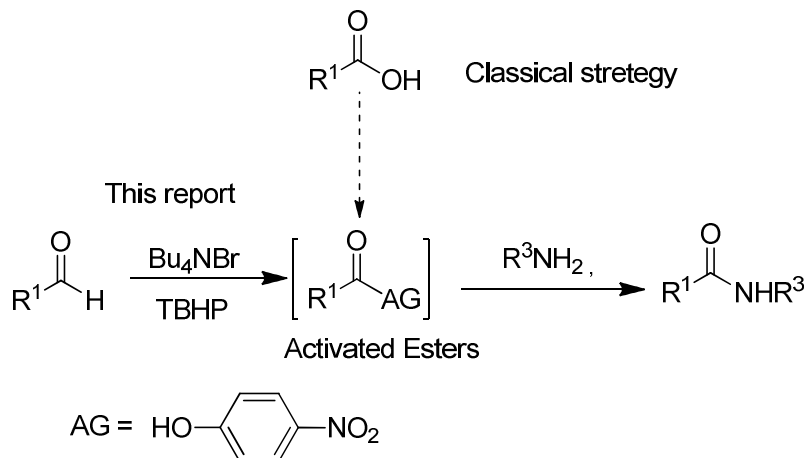
We herein demonstrate an efficient methodology for the amidation from aldehydes through *p*-nitro phenol ester activation using tetrabutyl ammonium bromide (TBAB) and tetrabutyl hydrogen peroxide (TBHP) in decane. Unlike the routine condensation chemistry using coupling reagents from the carboxylic acids, the present methodology offers advantages such as cheap catalyst, *in situ* activation from aldehydes that would preclude the stoichiometric chemical waste, a wide substrate scope etc. However, the present methodology suffers from a debilitating drawback that it could not be applied to the aliphatic aldehydes. In addition to the exploration of the catalyst, the electronic and steric factors are studied with appropriate selection of the substrates.

Keywords: Organo catalysis, Amidation, Activated ester, Tetrabutyl ammonium bromide

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INTRODUCTION

Ubiquitousness of amide and ester functionality makes the condensation reactions extremely important.¹ The classical condensation reaction is in between carboxylic acids and nucleophilic amines, alcohols and amino acids to produce amides, esters and peptides respectively.² Interestingly, most of these methods are through the activation of carboxylic acid into an activated form and then nucleophilic acylation.. Needless to mention that to make the activated ester, copious expensive coupling reagents have been developed that would produce stoichiometric amount of waste.³ But activation of aldehyde into an activated form for acylation has been recently started and largely being explored using transition metal catalysis and organocatalysis⁴. But, an important activating auxiliary i.e. *para* nitro phenolic esters, has not been attempted in the context of amide synthesis from aldehydes.⁵ Therefore, we wanted to make the *para* nitrophenol (PNP) esters *in situ* from aldehydes and thereby facilitate the amidation and esterification.



Scheme-1: Synthesis of amides and esters from Aldehydes

EXPERIMENTAL

General

Glassware was dried in an oven and cooled before use. Unless stated otherwise, all the materials obtained from commercial sources were used without any extra purification. Reactions were monitored by TLC on silica gel plates using UV-light and Iodine. The solvents used for recrystallization are distilled using the standard procedure. Evaporation of solvents was conducted under reduced pressure at 50°C. NMR spectra were reported on a Bruker 400 MHz NMR spectrometer. Chemical shifts (δ) and coupling constants (J) are given in ppm (parts per million) and Hz (Hertz), respectively.

Typical procedure for generality of reaction catalyzed by *n*-Bu₄NBr

The aldehyde (1 mmol, 1 equiv.) and *para* nitrophenol (1.5 mmol, 1.5 equiv.) were added to a 25 mL round bottom flask charged with a magnetic stirring bar and dissolved in ethyl acetate (3 mL). To this mixture, 10 mol% of *n*-Bu₄NBr (0.1 equiv) and 5.5 M *tert*-butyl hydroperoxide (TBHP) in decane (2.0 equiv) were added at room temperature. The reaction mixture was initially stirred at room temperature. It was noticed that the heating at 70°C accelerated the reaction. After completion of the reaction, the reaction mixture was cooled to room temperature and then added the respective amine (1.2 equiv.). The reaction was stirred at room temperature. Interestingly, the reaction was found to be complete within 20 min. Then the reaction mixture was further diluted with 10 mL EtOAc and then washed with 5% NaHCO₃ (3×10 mL). The product was almost isolated to be pure one, though it was recrystallized as per necessity.

- 1. N-Benzylbenzamide:** yield 91%, 193 mg; Colorless solid; ¹H NMR (400 MHz, CDCl₃) δ 7.78–7.73 (m, 2H), 7.42–7.30 (m, 4H), 7.36–7.28 (m, 4H), 4.61–4.59 (d, J = 4.0 Hz, 2H)
- 2. N-Benzyl-4-methoxybenzamide:** yield 87%, 209mg; Colorless solid; ¹H NMR (400 MHz, CDCl₃): 3.72 (s, 3H), 4.54 - 4.56 (d, 2H, J = 5.5 Hz), 6.84 - 6.87 (d, 2H, J = 7.5 Hz), 7.26 - 7.30 (m, 5H), 7.69 - 7.72 (d, 2H, J = 7.5 Hz)
- 3. N-Butylbenzamide:** yield 82%, 145 mg; Colorless solid; ¹H NMR δ (400 MHz, CDCl₃) 7.76-7.74 (d, J = 8.3 Hz, 2H), 7.37 - 7.51 (m, 3H), 6.35(br, s, 1H), 3.42 (m, J = 12.84, 2H), 1.62 (m, J = 14.35, 2H), 1.36-1.48(m, 2H), 0.99 (t, J = 6.79, 3H)
- 4. N-Butyl-4-nitrobenzamide:** yield 91%, 203 mg; Colorless solid; ¹H NMR δ (400 MHz, CDCl₃) 8.21-8.00 (d, J = 8.3 Hz, 2H), 7.92-7.90 (d, J = 8.3, 2H), 6.25 (br, s, 1H), 3.48 (m, J = 12.84, 2H), 1.65 (m, J = 6.79, 2H), 1.38 - 1.52 (m, , 2H), 1.0(t, J = 6.55, 3H)
- 5. 4-Bromo-N-butylbenzamide:** yield 80%, 204 mg; Colorless solid; ¹H NMR δ (400 MHz, d₆-DMSO) 8.00(s, broad, 1H), 7.75 (d, 2H, J = 7.6), 7.50 (d, J = 8.8, 2H), 3.30 (q, J = 12.84, 2H), 1.55 (m, J = 14.30, 2H), 1.20 - 1.48 (m, 2H), 0.95 (t, J = 6.79, 3H).
- 6. 4-Bromo-N-(tert-butyl)benzamide:** yield 108 mg (61%); Colorless solid; ¹H NMR δ (400 MHz, CDCl₃) 7.72-7.70 (d, J = 8.1 Hz, 2H), 7.37 - 7.45 (m, 3H), 5.84 (br, s, 1H), 1.46 (s, 9H).
- 7. Phenyl(piperidin-1-yl)methanone:** yield 96%, 181 mg; Colorless oil : ¹H NMR δ (400MHz, CDCl₃) 7.39 (brs, 5H), 3.72 (brs, 2H), 3.34 (brs, 2H), 1.68 (brs, 4H), 1.52 (br, 2H).
- 8. (4-Methoxyphenyl)(piperidin-1-yl)methanone:** yield 89%, 195 mg; Colorless oil : ¹H NMR δ (400MHz, CDCl₃) 7.36-7.38 (m, 2H), 6.89-6.92 (m, 2H), 3.82 (s, 3H), 3.69 (brs, 2H), 3.45 (brs, 2H), 1.64 (brs, 4H), 1.60 (br, 2H)
- 9. N-(p-Chlorobenzoyl) piperidine:** yield 81%, 180 mg; Colorless oil: ¹H NMR δ (400MHz, CDCl₃) 7.28-7.39 (m, 4H), 3.69 (brs, 2H), 3.33 (brs, 2H), 1.68 (brs, 4H), 1.52 (br, 2H).

10. Methyl 2-benzamidoacetate: yield 64%, 124mg; white solid. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.80 (m, 2H), 7.47 (m, 1H, $J = 7.6$ Hz), 7.34 (m, 2H, $J = 7.6$ Hz), 6.98 (bs, 1H), 4.18 (q, 2H, $J = 6.8$ Hz), 4.16 (d, 2H, $J = 5.2$ Hz), 1.25 (t, 3H, $J = 6.8$ Hz).

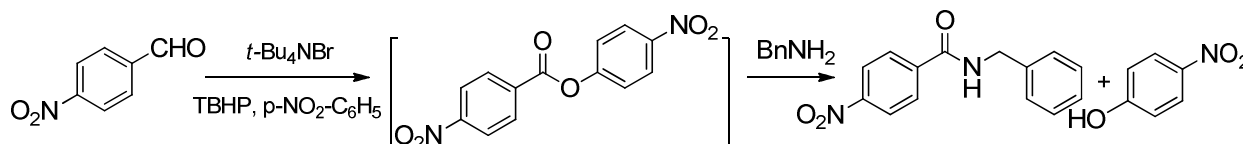
11. Methyl 2-(4-nitrobenzamido)acetate: yield 81%, 193 mg (); white solid. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.37-8.35 (d, 2H, $J = 8.4$ Hz), 7.96-7.94 (d, 2H, $J = 8.4$ Hz), 6.94 (bs, 1H), 4.28-4.21 (m, 4H), 1.31 (q, 3H, $J = 7.2$ Hz)

12. Methyl 2-benzamido-3-methylbutanoate: yield 59%, 138 mg; white solid. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.79 (m, 2H, $J = 7.2$ Hz), 7.48 (m, 1H, $J = 7.2$ Hz), 7.41 (m, 2H, $J = 7.2$ Hz), 6.69 (d, 1H, $J = 8.4$ Hz), 4.72 (m, 1H, $J = 8.8, 8.8$ Hz), 3.71 (s, 3H), 2.25 (m, 1H), 0.96 (m, 6H).

RESULTS AND DISCUSSION

As a model reaction we have taken benzaldehyde (1 equiv.) and *para* nitrophenol (1.5 equiv.) in an over dried round bottom flask. With catalytic amounts of simple tetrabutylammonium bromide (nBu_4NBr) as the precatalyst and a solution of tert-butyl hydrogen peroxide (TBHP) in decane as co-oxidant at room temperature, the reaction was continued to stir at specified temperature. After the disappearance of the spot corresponding to aldehyde in TLC we have added amount of benzyl amine (1.2 equiv.). The following Table-1 is the standardization results from which it is clear that 10 mol% of catalyst and 1.5 equivalent of PNP and 1.2 equivalent of amine.

Table-1: Standardization

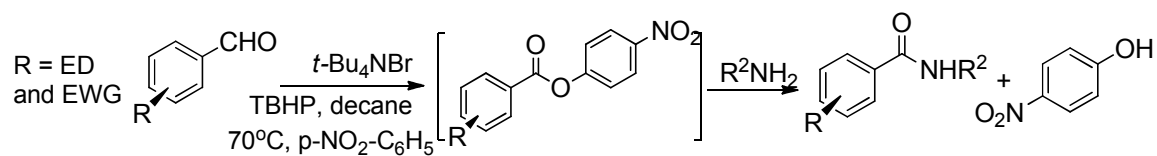


Entry	Bu_4NI	p-NO ₂ -C ₆ H ₅	Yield(%) ^a
1	50 mol%	0.3 equiv	32
2	30 mol%	0.5 equiv	48
3	10 mol%	1 equiv.	74
4	10 mol%	1.5 equiv	92

^a The yield refers to isolated yield after recrystallization. All the reactions were carried out using 1 equiv. of aldehyde in decane solvent. The product was characterized by matching the IR spectra and $^1\text{H-NMR}$.

In order to explore the scope of the present methodology for various molecules with different groups, we have studied with appropriate examples that are tabulated in the following Table-2. The methodology that we have developed is quite general for the condensation of aromatic aldehydes and aliphatic amines. But the attempts to carry out the transformation between aliphatic aldehydes and PNP did not progress under

Table-2: Substrate scope for amides



Entry	Aldehyde	Amine	Yield
1			91
2			87
3			82
4			91
5			80
6			61
7			96
8			89
9			81
10			64
11			81
12			59

the described conditions. However, PNP activated esters of carboxylic acids were very much known in the literature and could be used for the verities of amines to furnish respective amides. Though it was a limitation for the present methodology, it could have been successfully employed for the synthesis of aromatic amides. The aliphatic amines underwent the reaction smoothly. Notably, the present methodology is sensitive for the presence of electron donating and withdrawing effects of the substituents. The presence of electron donating group at para position of the aldehyde benzene ring decreased the yield than the case in which it is absent (entry 1 and 2, Table-2). The same effect was also seen in the entry 3 and 4 and entry 7, and 8, 9 also. On the other hand, the presence of an electron withdrawing group increased the yield of the final product (entry 3, 4 and 10 and 11, Table-2). Therefore, it can be generalized that the presence of electron donating group at 4th position would decrease the yield and the presence of an electron withdrawing group promotes the formation of the product in agreement with the theory. The low yield of the entry 12, Table-2, could be attributed for the steric bulkiness of the side chain of the amino acid. Additionally, entry 1, Table-2 has been attempted on 5g scale as well and interestingly, the product isolated was almost the same (90%). Furthermore, the activated ester is characterized for tor entry 1, table 2 using the IR spectra ¹H NMR and therefore, the formation of activated ester in the present case un debatable . All the products were well reported in the literature and each of the amide made was characterized from IR and¹H NMR. All the reactions were carried out with respect to 1 mole of the aldehyde. Every time the PNP ester was recovered and recycled which is an important aspect of the green chemistry practice.

CONCLUSION

In conclusion, we have demonstrated a method for the synthesis of amides and esters from the aldehydes through the well-known para nitro phenol ester activation. The yields are quite good and the reactions are faster. The problems that are associated with purification of these molecules with DCC/DMAP could be precluded by this method. Furthermore, the auxiliary that is used to activate, could have been recovered and re employed for several reactions. Even the reaction was carried out on a gram scale and the yield was found to be relatively good as well. The catalyst employed was catalytic (10mol %) and very cheap. The substrate scope is reasonably good and furnished the respective amides and esters in excellent yields. The present methodology limits its application to only the aromatic aldehydes and our attempts to carry out the transformation with aliphatic aldehydes were not fruitful. Importantly, the presence of electron withdrawing group on the aldehyde at an appropriate position, promoted the reaction whereas the presence of electron releasing group on it decreased the yield. Similar to this observation, the presence of electron withdrawing group on the phenolic part also increased the yield while the substituent with other effect decreased the yield.

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