



An Eco-friendly and Highly Efficient route for *N*-acylation under Catalyst-free Conditions

SOUAD OUARNA, HACÈNE K'TIR, SALAH LAKROUT, HAMIDA GHORAB,
AÏCHA AMIRA, ZINEB AOUF, MALIKA BERREDJEM and NOUR-EDDINE AOUF*

Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Sciences Faculty, Chemistry Department, Badji Mokhtar-Annaba University, Box 12, Annaba, 23000. Algeria.

*Corresponding author E-mail: noureddine.aouf@univ-annaba.dz

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ABSTRACT

An eco-friendly, simple, mild, chemoselective and highly efficient procedure for the acylation of primary and secondary amine function in various structurally and electronically aliphatic and aromatic compounds affording their corresponding *N*-Ac derivatives is developed. Mild conditions, simplicity and easier work-up are the main advantages of this method.

Key words: *N*-Acylation, amine, eco-friendly, protecting groups.

INTRODUCTION

In the last two decades, the development of mild, non-toxic, low cost, eco-friendly methodologies has received much attention in modern organic transformations.¹

The acylation of amines is fundamental chemical reaction for the production of important precursors, fine chemicals and pharmaceutical.² The *N*-acylation of amines also provides an efficient and low-cost means to protect their -NH groups in a multi-step organic process.^{3,4} It is, generally, achieved by the reaction between amines and

reagents containing acyl group. In the past few years, several methodologies were developed for *N*-acylation. This reaction is usually carried out with acylating reagent, such as acetic anhydride or acetyl chloride in the presence of acidic or basic catalysts in an organic medium. Recently, many methods were reported for on *N*-acylation of various structurally amines. The use of catalysts such as KF-Al₂O₃,⁵ ZnO,⁶ sodium formate,⁷ Amberlite IR₁₂O,⁸ FeCl₃,⁹ Al(OTf)₃,¹⁰ TiCl₃(OTf),¹¹ B(OCH₂CF₃)₃,¹² anhydrous NiCl₂,¹³ iodine¹⁴ and homogeneous Lewis acid such as ZnCl₂¹⁵ have been reported for the *N*-acylation under various conditions. Also, microwave irradiation technique¹⁶, thermally

decomposed Ni-Fe-hydrotalcite,¹⁷ heteropolyanion-based ionic liquids¹⁸ were used for the transformation of amines to their corresponding *N*-Ac derivatives. However, many of these methods suffered from various drawbacks such long reaction times, formation of side-products during base-catalyzed reactions.

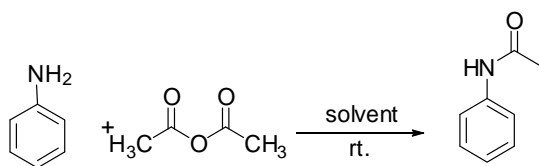
As a consequence of serious pollution problems, the adoption of new methods for minimizing the negative impact and process optimization is an urgent priority¹⁹. In this context, the development of mild and eco-friendly *N*-acylation reaction continue to attach a great deal attention.²⁰ An environmentally benign approach is described, where the *N*-Ac derivatives were prepared chemoselectively in water/micro-reaction system.^{21,22}

In continuation of our interest toward the development of useful green synthetic procedure,²³⁻²⁸ we report the *N*-acylation of various structurally amine, amino alcohols and sulfonamides under catalyst-free conditions.

RESULTS AND DISCUSSION

In order to find out the most effective reaction conditions, aniline was chosen as a model substrate. We first examined the influence of the solvent at room temperature. The reaction of aniline (1 mmol) with acetic anhydride (1.2 mmol) was studied using various solvents (THF, CH₂Cl₂, CHCl₃, Et₂O, EtOAc and H₂O) at room temperature (Table 1). As shown in Table 1: entries 01-07, the reaction was completed within 5-15 min, the acylated product was obtained in good to excellent yields and the nature of solvent does not influenced the reaction.

For typical reaction, we achieved the reaction without solvent and got the similar yields. Also, time necessary for completion of the reaction



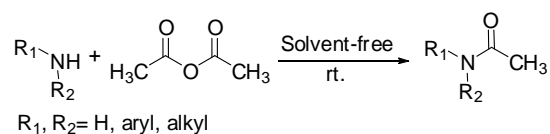
Scheme 1: *N*-acylation of aniline with acetic anhydride in various solvents

was the same, thus we observed that the solvent does not have any role in this reaction.

Table 1: Acylation of aniline in various solvents^a

Entry	Solvents	Time (min)	Yields (%) ^b
1	THF	6	75
2	CHCl ₃	5	79
3	CH ₂ Cl ₂	5	81
4	Et ₂ O	10	76
5	EtOAc	12	72
6	CH ₃ CN	7	78
7	H ₂ O	5	90
8	No solvent	5	89

^aReaction conditions: aniline (1mmol) acetic anhydride (1.2 mmol). ^bIsolated yield

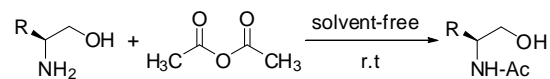


Scheme 2: *N*-acylation of amines with acetic anhydride in solvents free

Encouraged by the preliminary result and to increase the scope of this reaction, we attempt this study to aliphatic, aromatic and heterocyclic amines (Scheme 2). The results are summarized in Table 2. In all cases, we obtained the *N*-acylated product with good to excellent yields. The best result was obtained with *p*-nitroaniline as substrate, affording *N*-acylated product in 91% yield after 8 minutes.

The results showed that all products¹⁻¹⁹ are not influenced by the electron-withdrawing and electron-releasing substituents.

In order to expand the scope of this new protocol, we investigated the acylation to a variety of aminoalcohols (alaninol, valinol, leucinol and phenylalaninol) (Scheme 3).



Scheme 3: *N*-acylation of amino alcohols with acetic anhydride in solvents free

Table 2: Acylation of amines



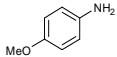
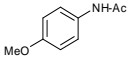
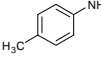
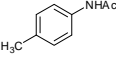
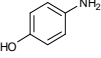
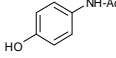

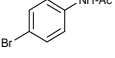

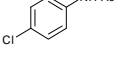






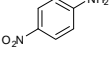
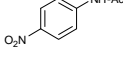




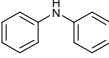
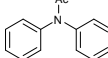






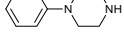
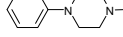


Entry	Substrate	Product	Time (min)	Yield (%)
01			5	86
02			12	85
03			13	84
04			13	87
05			6	86
06			8	79
07			6	80
08			8	81
09			6	85
10			8	91
11			10	80
12			5	78
13	$\text{H}_3\text{C}-\text{NH}_2$	$\text{H}_3\text{C}-\text{NH}-\text{Ac}$	15	76
14			12	76
15			15	70
16			13	68
17			15	72
18			13	70
19			15	72

Table 3: Acylation of amino alcohols

Entry	Substrate	Product	Time (min)	Yield (%)
20			10	84
21			12	85
22			8	87
23			10	90

As it can be seen from results in Table 3, the reaction worked very well, and it was quite satisfactory considering that it was carried out without the use of any base, catalyst and solvent. The isolated yields of products (Table 3, Entries 20-23) were in the range of 85-90% after few minutes of reaction.

The simplicity and the chemoselectivity of this method can be determining of its application in the organic synthesis and particularly in peptide synthesis.

It is noteworthy that the reaction preserves the regioselectivity and stereochemical integrity of *N*-acyl amino alcohols, where the configuration of the chiral center was not affected by the conditions of reaction and the optically pure *N*-acyl derivatives were confirmed by optical rotation and comparison with literature.

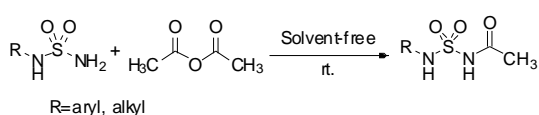
The structures of all compounds were unambiguously confirmed by spectroscopic

methods (IR, ^1H , ^{13}C NMR and elemental analysis). For the resulting compounds (Table 3, Entries 18-21), IR spectra showed bands at 1650-1700 cm^{-1} ($\text{C}=\text{O}$) acetyl. ^1H -NMR spectra showed the shift of proton corresponding to CH_3 acetyl at 2.25 ppm.

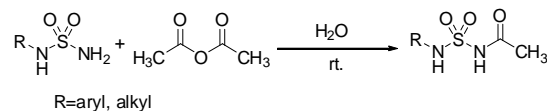
To increase the scope of this reaction, we extended this study to sulfonamides²⁹ (scheme 04).

Unfortunately moderate yields of the corresponding products were formed with longer reaction times (table 04). Thus we thought that the sulfonamide require the use of a small amount of solvent.

For this reason and after referring to table 1, we decide to use the solvent who showed the best results; water. We treated sulfonamide (1mmol) in water with acetic anhydride in the absence of any catalyst (scheme 05). We choose *N*-benzyl sulfonamide as a model substrate. The reaction was complete in 8 minutes and expected product was obtained in (92%).

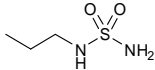
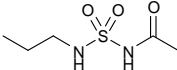
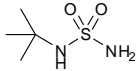
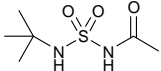
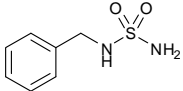
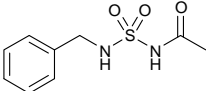
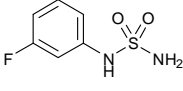
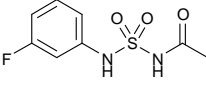
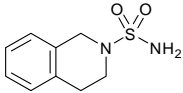
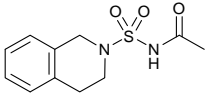
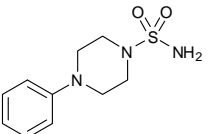
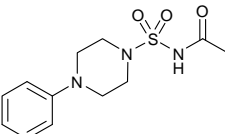
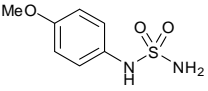
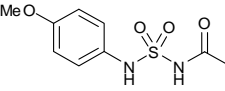
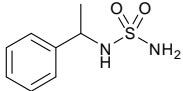
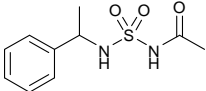


Scheme 4: *N*-acylation of sulfonamides with acetic anhydride under solvents free conditions



Scheme 5: *N*-acylation of sulfonamides with acetic anhydride in water

Table 4: Acylation of sulfonamide

Entry	Substrate	Product	Time (min)	Yield (%)
24			14	90
25			12	90
26			8	92
27			9	90
28			8	90
29			10	90
30			9	88
31			12	87

EXPERIMENTAL

General

All commercial chemicals and solvents were used without further purification. Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in a 250 MHz Brücker spectrometer. Chemical shifts are reported in (ppm) units with tetramethylsilane (TMS) as reference. All coupling constants (J) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and combinations of these signals. All reactions were monitored by

thin layer chromatography (TLC) on silica Merck 60 F254 percolated aluminium plates. Column chromatography was performed on Merck silica gel (230-400 mesh).

Typical experimental procedure for the synthesis of N-Acylated amines, amino alcohols and sulfonamides

In a 50mL round-bottomed flask, a mixture of amine or amino alcohol (1 mmol) and acetic anhydride (1.2 mmol) was stirred at room temperature for the appropriate time. After completion of the reaction, as monitored by TLC,

the reaction mixture was dissolved in ether (5 mL) and was allowed to stand at room temperature for 1 hour. During this time, crystal of product formed, which were collected by filtration.

In the case of solid substrates (sulfonamides), the same protocol was used. However, the use of water was required for the solubility of the mixture. The *N*-acylated sulfonamides were collected by crystallization from diethyl ether.

CONCLUSIONS

In summary, we developed new and efficient acylation of primary and secondary amines,

aminoalcohols and sulfonamides. This new process has several advantages, such as high yield, short reaction times, low cost and simple experimental procedure. This method provides a green and much improved protocol over the existing methods.

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REFERENCES

- (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.
(b) J. S. Wilkes, *Green Chem.* **2002**, *4*, 73.
(c) Zhang, Q.; Zhang, S.; Deng, Y. *Green Chem.* **2011**, *13*, 2619.
- (a) Hallettand, J. P.; Welton, T. *Chem. Rev.* **2011**, *111*, 3508.
(b) Zhang, Q.; Zhang, S.; Deng, Y. *Green Chem.* **2011**, *13*, 2619.
(c) Taylor, J. E.; Bull, S.D. In *Comprehensive Organic Synthesis II*, 2nd edn.; Elsevier Ltd. **2014**; Vol 6, p 427.
- Greene, T. W., Wuts, P. G. M. In *Protective Groups in Organic Synthesis*; 3rd edn.; Wiley & Sons: New York; **2007**.
- KocieDski, P. J. In *Protecting Groups*; Georg Thieme Verlag: New York, **1994**.
- Mihara, M.; Ishino, Y.; Minakara, S.; Komatsu, M. *Synthesis*, **2003**, 2317.
- Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652.
- Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* **2010**, *51*, 2319.
- Bhojgowd, M. R. M.; Nizam, A.; Pasha, M. A. *Chin. J. Catal.* **2010**, *31*, 518.
- Likhar, P. R. *Journal of Molecular Catalysis A: Chemical*, **2009**, *302*, 142.
- Kamal, A.; Khan, M. N. A.; Reddy, K. S.; Srikanth, Y. V. V.; Krishnaji, T. *Tetrahedron Lett.* **2007**, *48*, 3813.
- Firouzabadi, H.; Iranpoor, N.; Farahi, S.; *J. Mol. Catal. A*, **2008**, *289*, 61.
- Lanigan, R. M.; Starkov, P.; Sheppard, T. D. *J. Org. Chem.* **2013**, *78*, 4512.
- Meshram, G.; Patil, V. D. *Synth. Commun.* **2009**, *39*, 4384.
- Phukan, K.; Ganguly, M.; Devi, N. *Synth. Commun.* **2009**, *39*, 2694.
- Shekhar, A. C.; Kumar, A. R.; Sathaiah, G.; Paul, V. L.; Sridhar, M., Rao, P. S. *Tetrahedron Lett.* **2009**, *50*, 7099.
- Wang, X. -J.; Yang, Q.; Liu, F.; You, Q. -D.; *Synth. Commun.* **2008**, *38*, 1028.
- Choudhary, V. R.; Dumbre, D. K. *Catalysis Communications*, **2011**, *12*, 1351.
- Chen, Z.; Fu, R.; Chai, W.; Zheng, H.; Sun, S.; Qiang, L.; Yuan, R. *Tetrahedron*, **2014**, *70*, 2237.
- (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, **1988**.
(b) Gawande, M. B.; Bonifácio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, *42*, 5522.
(c) Gawande, M. B.; Bonifácio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *ChemSusChem* **2014**, *7*, 24.
(d) Matlack, A. S.; In *Introduction to Green Chemistry*, Marcel Dekker Inc., New York, **2001**.

- (e) Lancaster, M. In *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, Cambridge, **2002**.
- (f) Clark, J. H.; Macquarrie, D. J.; eds.; *Handbook of Green Chemistry & Technology*; Blackwell Publishers, Oxford, **2002**.
- (g) Grieco, P. A. Eds.; In *Organic Synthesis in Water*; Blackie academic & professional; London, **1998**.
- 20 (a) Grieco, P. A. Eds.; *Organic synthesis in water*. London: Blackie academic & professional; London, **1998**.
- (b) Pappas, K.; Zhang, X.; Tang, W.; Fang, S. *Tetrahedron Lett.* **2009**, *50*, 5741.
- (c) Chen, Z.; Fu, R.; Chai, W.; Zheng, H.; Sun, S.; Qiang, L.; Yuan, R. *Tetrahedron*, **2014**, *70*, 2237.
21. Fruzsina, S.; Daniel, S.; Zoltan, N. *RSC Adv.* **2014**, *4*, 3883.
22. Sato, M.; Matsushima, K.; Kawanami, H.; Yokoyama, T.; Ikuhsima, Y.; Maro Susuki, T. *Lab Chip*, **2009**, *9*, 2877.
23. Cheraïet, Z.; Hessainia, S.; Ouarna, S.; Berredjem, M.; Aouf, N. -E. *Green Chem. Lett. Rev.* **2013**, *6*, 211.
24. Amira, A.; K'tir, H.; Berredjem, M.; Aouf, N. -E. *Monatsh. Chem.*, **2014**, *145*, 509.
25. Belghiche, R.; Cheraïet, Z.; Berredjem, M.; Abbessi, M.; Aouf, N. -E. *Eur. J. Chem.* **2012**, *3*, 305.
26. Nadia, K.; Malika, B.; Nawel, K.; Belghit, M. Y.; Regaïnia, Z.; Aouf, N. E. *J. Heterocycl. Chem.* **2004**, *41*, 57.
27. Lakrou, S.; K'tir, H.; Amira, A.; Berredjem, M.; Aouf, N. -E. *RSC Adv.*, **2014**, *4*, 16027.
28. K'tir, H.; Amira, A.; Berredjem, M.; Aouf, N. -E. *Chem. Lett.* **2014**, *43*, 851.
29. (a) Berredjem, M.; Bouasla, R.; Aouf, N. -E.; Barbey, C. *X-Ray Structure Analysis Online.* **2010**, *26*, 13.
- (b) Boufas, W.; Dupont, N.; Berredjem, M.; Berrezag, K.; Becheker, I.; Berredjem, H.; Aouf, N. -E. *J. Mol. Struct.*; **2014**, *1074*, 180.