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# REGIOSELECTIVE N-ACYLATION OF HETEROCYCLIC AMINES UNDER DRY CONDITIONS CATALYZED BY A NATURAL CLAY

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**ABSTRACT**: An environment friendly, general, rapid, and one-pot convenient procedure for N-acylation (acetylation and benzoylation) of nitrogenous heterocyclic compounds have been reported using stoichiometric amounts of heterocyclic amines and acetyl chloride or benzoyl chloride under solvent-free conditions catalyzed by a naturally available reusable clay (clay used by the traditional potters of Assam, India) at room temperature. The general efficiency of the method is evident from the variety of the N-based heterocycles, including both five and six membered rings, resulting in the corresponding N-acyl heterocycles, which react in excellent yields (69-97%) within a very short time (4-35 mins.).

**Key words:** Acetylation, benzoylation, acetyl chloride, benzoyl chloride, N-based heterocyclic compounds, potter's clay.

## INTRODUCTION

The growing awareness of environmental issues has focused attention on the need for greener and more sustainable technologies in the chemical industry [(a) M Djebabra et. al., 2006 (b) P Roy, 2009 (c) S K Sharma, 2010]. The numbers of environmental laws and regulations have increased over the years, and more specific regulations have been set in order to provide a safe environment. N-acetylation and N-benzoylation are among the most widely used transformations in organic synthesis [(a) T W Greene et. al., 1999 (b) R Dumeunier, 2004]. They are common motifs in pharmaceutical and agrochemical research (a) B M Choudary et. al. 2005 (b) P Cozzi et. al., 1993]. In practical terms, acylation involves the following categories: (a) direct reaction of an amine with an acid, (b) reaction of an readily available acid derivative (e.g., simple methyl ester) with an amine, (c) formation of an activated carbonyl compound (e.g., acid chloride, anhydride, or active ester) followed by condensation with an amine, and (d) one-pot reaction of a carboxylic acid with an amine in which a coupling reagent activates the acid component in situ. Acid halides and acid anhydrides are commonly used for N-functionalization of amines [(a) Y Ishii et. al., 1996 (b) K Phukan et .al. 2009 (c) R C Larock, 1989]. The widely used Schotten-Baumann condition suffers from the drawback that hydrolysis of acetyl chloride and benzoyl chloride is a significant competing side reaction, so a strict maintenance of pH is required. However, N-functionalization of heterocyclic compounds is a long standing problem, which is far from satisfactorily solved. The above methodologies cannot be applied for the N-functionalization of heterocycles satisfactorily as C-functionalization often competes (T. Satoh et. al., 2007). One major environmental risk in using acetic anhydride is that it is highly explosive and carcinogenic. Not surprisingly, numerous efforts have been devoted for the preparation of N-functionalized heterocycles [(a) T L Gilchrist, 2007 (b) M R Grimmet, 1997 (c) N Zheng et. al., 2007 (d) M Balogh et. al., 1993]. Despite of these efforts, the preparation of N-acylated heterocyclic compounds in regioisomerically pure form remains a challenging issue. Recently, the uses of solid acidic catalysts like clays, zeolites, and ion-exchange resins, have received much research interest in different areas of organic synthesis because of their environmental compatibility, reusability, greater selectivity, noncorrosiveness, low cost, and ease of handling [(a) K Phukan et. al., 2011 (b) G Bram et. al., 1992 (c) J H Clark, 2002 (d) D Habibi et. al. 2007 (e) T S Li et. al., 1997]. In continuation of our effort to find out mild and general methodology for N-functionalization of heterocycles (K Phukan, et. al. 2009), herein we intend to report a general, rapid, and one-pot convenient procedure for regioselective N-acylation (acetylation and benzoylation) N-H containing heterocyclic compounds using stoichiometric amounts of the substrates and acetyl chloride/benzoyl chloride under solvent-free conditions catalyzed by a locally available clay (clay used by the traditional potters of Assam, India) at room temperature (Scheme 1).

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The general efficiency of the reactions is evident from the variety of the N-containing heterocycles including both five and six membered rings, which react in excellent yields (69-97%) within a very short time (4-35mins). In one of our earlier works, characterization of the clay using XRD, SEM-EDXRA, thermal analysis, FT-IR spectra and elemental analysis revealed it to be an iron rich clay with kaolinite as the major component (K Phukan et. al., 2011). The synthesized products were characterized by melting points, TLC, FT-IR and <sup>1</sup>H NMR data. The present method has the specificity that naturally available clay can be used as catalyst after simple mechanical treatment instead of more costly commercial clays. Further it has many obvious advantages over those reported in the literature including high efficiency, comparable yields with the commercial clay catalysts, cost efficiency, operational simplicity, environmental benignity, and the possibility of recycling the solid clay. The solid clay catalyst used in the first cycle of reactions was successfully recovered and reused in the subsequent cycles, showing almost no decrease in catalytic activity.



Scheme 1

## MATERIALS AND METHODS

The clay sample was obtained from a local traditional potter of Assam,India. The sample was dried, grounded in a mortar and then sieved as to pass through 200 mesh ASTM sieve and retain on 300 mesh. 50g of this clay sample was stirred well in a 1000mL sedimenting cylinder with 1000mL distilled water, allowed to stand for 4 h and 250 mL of the suspension was removed and evaporated. The dry mass was again stirred with 100 mL ethanol to dissolve any organic matter present, filtered and dried. The clay was then grounded and heated in an air oven at 60°C, characterized (K Phukan et. al., 2011) and used as catalyst. All chemicals used were of LR grade (S. d. Fine Chem. Ltd.). The completion of reactions and purity of the products were checked on silica gel G TLC plates of 2mm thickness using n-hexane and ethyl acetate as solvent system. Melting points were determined by using a Labtronics digital auto melting point apparatus and were therefore uncorrected. The visualization of spots was carried out in an iodine chamber. The IR spectra of the synthesized compounds were recorded in the 4000-450cm<sup>-1</sup> ranges using KBr discs on a Shimadzu FTIR-8400 spectrophotometer and <sup>1</sup>H NMR spectra were recorded on a Bruker DRX-400 MHz spectrometer in CDCl<sub>3</sub> using TMS as an internal standard.

#### General procedure for N-benzoylation/ acetylation

The heterocyclic substrate (1.05 mmol) to be N-benzoylated was added in pinches to a stirred mixture of benzoyl chloride (1.05 mmol) and the clay (0.5g) at room temperature, and stirring continued between two additions for the appropriate time as monitored by thin-layer chromatography (TLC). The reaction mixture was then repeatedly washed with ethanol (3x20mL) and the filtrate was evaporated to afford crude products, which were recrystallized from ethanol. Melting points were taken and spectral data (IR and <sup>1</sup>H NMR) were recorded. The residual clay was treated with acetone, washed twice with distilled water and recycled to use in the subsequent reactions. For N-acetylation, the same procedure was followed using acetyl chloride remaining other conditions identical. For substrates 2.15, 2.16 and 2.17, 3.05 mmol of the reagents were needed to get difunctionalized products. Synthesized compounds (Table 1&2) were characterized by comparing with literature data [(a) Aldrich Catalog of Fine Chemicals, 1990-1991 (b) Dictionary of Organic Compounds, 5<sup>th</sup> & 6<sup>th</sup> eds, Chapman and Hall, 1982 & 1997].

Spectral characterization data of some of the representative products are given below:

**Compound 1.1** IR (KBr, cm<sup>-1</sup>) 1725, 1690 (C=O<sub>str</sub>), 3037 (C-H<sub>str</sub>, Ar-H), 1622 (C=N<sub>str</sub>), 917(C-N<sub>str</sub>);

<sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm) 7.25 (s, 1H, Ar-H), 7.65 (d, 2H, Ar-H), 8.1 (m, 5H, Ar-H).

**Compound 1.2** IR (KBr, cm<sup>-1</sup>) 1730, 1685 (C=O<sub>str</sub>), 2880 (C-H<sub>str</sub>), 1605 (C=N<sub>str</sub>), 920(C-N<sub>str</sub>);

<sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm) 1.96(s, 3H, CH<sub>3</sub>-C=O), 9.11 (s, 2H, Ar-H), 7.82(s, 1H, Ar-H).

**Compound 2.7b** IR (KBr, cm<sup>-1</sup>) 922 (C-N<sub>str</sub>), 3030 (aromatic ring), 2885 (C-H<sub>str</sub>), 1620 (C=C<sub>str</sub>), 520 (NO<sub>2</sub>);

<sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm) 1.98(s, 3H, CH<sub>3</sub>-C=O), 9.01 (s, 1H, Ar-H), 7.82(s, 1H, Ar-H).

**Compound 2.11b** IR (KBr, cm<sup>-1</sup>) 3038 (C-H<sub>str</sub>, Ar-H), 1725, 1690 (C=O<sub>str</sub>), 1605 (C=N<sub>str</sub>), 915(C-N<sub>str)</sub>, 520 (NO<sub>2</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ ppm) 1.99(s, CH<sub>3</sub>-C=O, 3H), 8.39-8.21(m, 4H, H- Ar- NO<sub>2</sub>), 7.62-7.43(m, 4H, Ar-H),

7.02-7.10 (m, 6H, Ar-H).

**Compound 2.13a** IR (KBr, cm<sup>-1</sup>) 1680 (C=O<sub>str</sub>), 3032 (C-H<sub>str</sub>, Ar-H), 725(C-Cl<sub>str</sub>), 1619(C=N<sub>str</sub>), 909(C-N<sub>str</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$  ppm) 8.06(d, 2H, J = 8.0Hz), 7.60-7.42(m, 4H, H- Ar- NO<sub>2</sub>), 7.40-7.06(m, 8H, Ar-H). **Compound 2.18b** IR (KBr, cm<sup>-1</sup>) 915(C-N<sub>str</sub>), 2965 (C-H<sub>str</sub>, CH<sub>3</sub>), 1710, 1687(C=O<sub>str</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>,  $\delta$  ppm) 1.91(s, CH<sub>3</sub>-C=O, 3H), 0.94 (s, -CH<sub>3</sub>, 6H).

## **RESULTS AND DISCUSSION**

To find out the optimized reaction condition we have tried benzoylation of imidazole using benzoyl chloride at first. Interestingly, predominant amount of N-benzoyl imidazole was formed over C-benzoyl product as revealed by the disappearance of the peak at  $\delta$  7.7 ppm (1N-H) and appearance of a new peak at  $\delta$  8.1 ppm (5H, Ar-H) in the <sup>1</sup>H NMR spectrum (entry 1.1). Formation of N-benzoylimidazole is also confirmed by the disappearance of the band at 3377 cm<sup>-1</sup> (N-H<sub>str</sub>) and appearance of a new band at 1725 cm<sup>-1</sup> (C=O<sub>str</sub>) in the FT-IR spectra of the product. 0.5g of the clay with 1.05 mmol of imidazole and 1.05 mmol of benzoyl chloride gave a maximum of 96% N-benzoyl imidazole within 5 min at room temperature. The recyclability of the clay was investigated by reusing it for N-benzoylation of imidazole but gradual decrease in activity was observed in the subsequent cycles. The process was extended towards the functionalization of imidazole using acetyl chloride, methyl iodide, chlorobenzene and benzyl chloride turn by turn in place of benzoyl chloride remaining other conditions identical. Expectedly N-functionalized products were obtained in moderate to excellent yields (85-97%) within a very short time (4-22 min) (Table 1).

Entry	Reagent(s) <sup>a</sup>	Product (s) <sup>b</sup>	Time/min <sup>c</sup>	Isolated yield(s)/%			
Entry				1 <sup>st</sup> cycle	2 <sup>nd</sup> cycle	3 <sup>rd</sup> cycle	
1.1	Benzoyl chloride	N-COPh	5	96	95	92	
1.2	Acetyl chloride	N-COCH3	4	92	90	90	

<sup>a</sup>1.05 mmol, <sup>b</sup>1.05 mmol, analysed by spectral data, <sup>c</sup>monitored by TLC

Encouraged by the above results our hypothesis was successfully implemented to the N-functionalization of a diverse set of N-based heterocyclic compounds using this clay catalyst, and the results are summarised in Table 2. Interestingly, heterocycles having strong electron withdrawing groups also gave satisfactory yields in the investigation (entries 2.3, 2.5, 2.6, 2.11, 2.13etc.). For substrates 2.15, 2.16 and 2.17, 3.05 mmol of the reagents were needed to get difunctionalized products as these substrates contain two N-H groups in the heterocycles. This reveals the strict maintenance of stoichiometries of the reactions. Faster reactivity over the oxidative coupling methodologies (B M Choudary et. al., 2005) and regioselectivity are other attributes of this innovative methodology. As shown in Table 2, benzimidazole, indole, pyrrole, piperidine, carbazole, phthalimide and a number of C-substituted imidazoles responded to this generalized pathway to give the corresponding N-functionalized products in good yields. It is significant to note that neither the substituted groups like –NO<sub>2</sub> nor the ring carbons were substituted establishing its regioselective nature (entries 2.3, 2.5, 2.13, 2.16, 2.17 etc.). This new method also rules out the necessity for use of strong basic support for activation of the deactivated reagents like benzoyl chloride, acetyl chloride etc.[(a) B M Choudary et. al., 2005 (b) B Das et. al., 2007 (c) S U Son et. al., 2004 (d) B M Choudary et. al., 2002].

Table 2. N-ad	cvlation of	different N	-based	heterocyl	es using	clay o	catalyst at	room	temperature
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Entry	Substrate(s)	Product(s)*	Time/min (isolated yield/%)		
2	1	2	$R = -COPh^a$	-COCH <sub>3</sub> <sup>b</sup>	
2.1			10(93)	12(87)	
2.2			14(85)	20(92)	
2.3	NNO2 H		15(87)	20(82)	
2.4	N-H o	N-R O	10(94)	25(92)	
2.5	NO2 N-H	NO <sub>2</sub> O N-R	30(80)	35(75)	

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2.6			35(72)	30(69)
2.7			30(80)	35(94)
2.8	∧ ⊢ H		20(70)	25(75)
2.9**	Ph Ph	Ph Ph	15(94)	20(97)
2.10**	N N H H	N N R R	15(90)	20(92)
2.11**	Ph Ph H H H H H H H H H H	Ph Ph R R R $N_{R}$ $NO_{2}$	35(80)	32(65)
2.12**	KN CH₃	CH <sub>3</sub>	20(91)	25(96)
2.13**			30(75)	35(64)
2.14**	Ph Ph H H OMe		35(80)	35(75)
2.15	N N N N N N N N N N N N N N N N N N N		25(80)	25(75)
2.16***	Ph N H O		20(82)	20(85)
2.17***	Ph H Ph N O H	Ph R Ph N R	35(80)	30(75)
2.18***	H <sub>3</sub> C H H <sub>3</sub> C N H <sub>3</sub> C N H	H <sub>3</sub> C R H <sub>3</sub> C N R	35(70)	30(78)

\*Structure elucidation done by spectra (IR and <sup>1</sup>H NMR) data.

\*\*Substrates were prepared as described in the reference no.21.

\*\*\*Substrates were prepared as described in the reference no.18.

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#### REFERENCES

Aldrich Catalog of Fine Chemicals. (1990-1991). Balogh M, Laszlo P (1993), In Organic Chemistry Using Clay, Spinger-Verlag, New York.

Bram G, Loupy, and Villemerin D (1992), In Solid Support and Catalyst in Organic Chemistry, Ellis Horwood, London, UK.

Choudary B M, Madhi S, Chowdari N S, Kantam M L, and Sreedar B (2002) J. Am. Chem. Soc. 124, 4127. Choudary B M, Sridhar C, Kantam M L, Venkanna G T, and Sreedhar B (2005), J. Am. Chem. Soc. 127,9948. Clark J H (2002), Acc. Chem. Res. 35,791

- Cozzi P, Carganico G, Fusar D, Grossoni M, Menichincheri M, Pinciroli V, Tonami R, Vaghi F, and Salvati P (1993), J. Med. Chem. 36,2964.
- Das B, Srinivas Y, Holla H, Krishnaiah H, Narender R (2007), Chem. Lett. 36(10), 1270.Dictionary of Organic Compounds, 5<sup>th</sup> & 6<sup>th</sup> eds, Chapman and Hall. (1982 & 1997).
- Djebabra M, Bentrcia T, Saadi S, and Bahmed L (2006), Management of Environmental Quality: An International Journal, 17(2), 157-169.
- Dumeunier R, Marko I E (2004), Tetrahedron Lett. 45,825. Gilchrist T L (2007), In Heterocyclic Chemistry, Pearson Education Ltd., Dorling Kindersley (India) Pvt. Ltd. p.298.
- Greene T W, and Wuts P G M (1999), In Protective groups in Organic Synthesis, 3rd ed., John Wiley and Sons: New York, p.36.
- Grimmet M R (1997), In Imidazole and benzimidazole synthesis, best synthetic methods (Ed.: O. Meth-Cohn), Academic, London.
- Habibi D, Davood, Mahmoodi, Nosratollah, Marvi O, and Omid (2007). Canadian J. Chem. 2, 81.
- Ishii Y, Takeno M, and Kawasaki Y (1996), J. Org. Chem. 61, 3088
- Larock R C (1989), In Comprehensive organic transformations, VCH Publishers Inc.: New York, p. 980.
- Li T S, Li S H, Li J T, and Li H Z (1997), "Montmorillonite clay catalysis. Part 2.1 an efficient and convenient procedure for the preparation of acetals catalyzed by montmorillonite K-10". J. Chem. Res.(S), 26.
- Phukan K, and Devi N (2011). "Microwave-Assisted Dry Synthesis of 2-Amino-1H-imidazoles Supported by a Natural Clay". Der Chemica Sinica. 2(6), 32-41.
- Phukan K, and Devi N (2011). "Greener and Versatile Synthesis of Bioactive 2-nitroimidazoles Using Microwave Irradiation". J. Chem. Pharm. Res. 3(6), 1037-1044.
- Phukan K., Ganguly M, and Devi N (2009) "M ild and Useful Method for N-acylation of Amines". Synth. Commun. 39, 2694-2701.
- Phukan K, Jain A, and Devi N (2011) "Characterization of an Iron-rich Kaolinite Clay and Its Application as Reusable Heterogeneous Catalyst for the Microwave-Mediated Solventless Synthesis of N-containing Heterocycles". Res. J. Chem. Environ. 15(1), 86-91.
- Roy P, Nei D, Orikasa T, Xu Q, Okadome H, Nakamura N, and Shiina T (2009) "A review of life cycle assessment (LCA) on some food products". Journal of Food Engineering, 90, 1-10.
- Satoh T, and Miura. M (2007), "Catalytic Direct Arylation of Heteroaromatic Compounds". Chem. Lett. 2, 200.
- Sharma S K (2010) "Green Chemistry for Environmental Sustainability. Series: Advancing Sustainability Through Green Chemistry and Engineering", CRC Press, Boca Raton, FL.
- Son S U, Park I K, Park J, and Hyen T (2004) "Synthesis of Cu<sub>2</sub>O Coated Cu Nanoparticles and Their Successful Applications to Ullmann-type Amination Coupling Reactions of Aryl Chlorides". Chem. Commun. 7, 778.
- Zheng N., Anderson K W, Huang X, Nguyen H N, and Buchwald S L (2007) "A Palladium-Catalyzed Regiospecific Synthesis of N-Aryl Benzimidazoles". Angew. Chem. Int. Ed. 46,7509.