Research Article

SYNTHESIS OF N-ACYL HETEROCYCLES USING CONVENTIONAL AND MICROWAVE-ASSISTED DRY MEDIA TECHNIQUE

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Received on: 07-05-2008; Accepted on :22-08-2008

ABSTRACT

A rapid and efficient synthesis of acyl derivatives of N-heterocycles has been performed via the Schotten Bauman reaction. Reactants impregnated individually, on basic alumina, and exposed to microwave irradiation in the presence of base as a catalyst, wherein not only the reaction times have been brought down from hours to minutes in comparison to conventional heating but also the yields of products were improved. New N-acyl heterocycles have been prepared for the first time by microwave-assisted dry media technique and conventional method.

Key words: N- Acyl-heterocycles, microwave, dry media, solventless, conventional.

INTRODUCTION

Improving drug research and development (R&D) productivity is one of the biggest tasks facing the pharmaceutical industry. Lead compound optimization and medicinal chemistry remain the bottlenecks in the drug discovery process. Microwave-assisted synthesis has evolved as a highly versatile, revolutionary technique that allows more rapid, efficient synthesis and screening of chemical substances to identify compounds in lead compound optimization. It has received considerable attention over the years due to the eminent advantages [1,2,3] like shorter reaction times (typically from days or hours to minutes or seconds.), higher yields, high purity of resulting products, simple reaction conditions, faster optimization of reaction conditions, low cost, simplicity in processing, handling and feasibility[7,8,9,10]. In addition, the use of supported reagents coupled with microwave irradiation has gained special attention due to its ecofriendliness and safety[4].

Many literature reports have revealed that nitrogen heterocycles possess immense biological activities. Thus it was planned to synthesize a series of N-acyl derivatives of the nitrogen heterocycles by the conventional method and the microwave-assisted method using supported reagents (dry media method) and to compare the two methods for parameters like reaction times and percent yields of compounds.

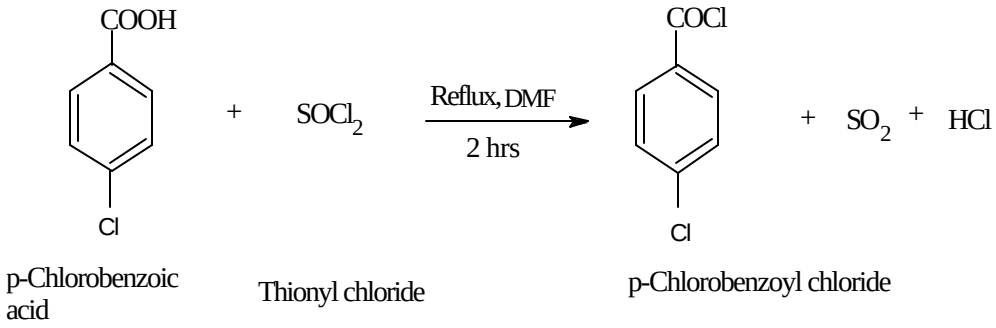
MATERIALS AND METHODS

The chemicals and solvents required for the research work were procured from S. D. Fine Chemicals, Mumbai and CDH Laboratories, Mumbai.

General Procedure

In the present work eight N-acyl heterocycles were synthesized using Schotten Bauman reaction by conventional method (scheme I). The purity of compounds was determined by TLC, HPLC and the structures of compounds were confirmed by IR and ^{1}H NMR spectroscopy techniques. The same compounds were synthesized

Step A: Synthesis of acid chlorides



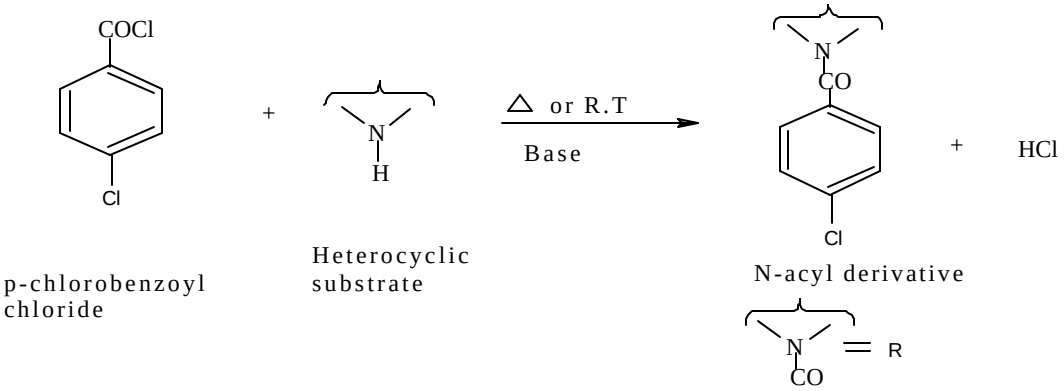
using microwave- assisted dry media method (scheme II) and compared for reaction time and yield with conventional method.

Scheme I

Synthesis of N-acyl derivatives of heterocyclic substrates by conventional method was carried out in two steps.

Step A: Synthesis of acid chlorides

p-Chlorobenzoic acid (1g, 6.4 mmole) was placed in a 100 ml round bottom flask, equipped with a reflux condenser and calcium chloride guard tube. To this was added thionyl chloride (3- 4 ml) in small portions with constant shaking. One or two drops of Dimethylformamide were also added. The reaction mixture was refluxed on a water bath for two hours. The excess of thionyl chloride was distilled off to obtain p-Chlorobenzoyl chloride. p-Chlorobenzoylchloride thus formed was used immediately for the next step.



Step B: Synthesis of N-acyl derivatives

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In a 100 ml round bottom flask, equipped with a reflux condenser and a calcium chloride guard tube was placed a mixture of heterocyclic substrate (6.4 mmole for 1:1 molar ratio of acid chloride: heterocyclic substrate and 3.2 mmole for 2:1 molar ratio of acid chloride: heterocyclic substrate) and triethylamine (6.4 mmole) or pyridine (3.84 mmole) in 10 ml of a suitable solvent. To this solution was added acid chloride (6.4 mmole), slowly with constant stirring, during 30 minutes period. The mixture was heated at different reaction conditions for an appropriate time till the reaction was complete as monitored by TLC. After cooling to room temperature the product was extracted with chloroform (3x15 ml). The combined extracts were washed with saturated sodium bicarbonate

solution, dilute hydrochloric acid and finally with water. The extract was dried over anhydrous sodium sulphate and the solvent was distilled off to get the required product. The product was recrystallized from a suitable solvent.

In the conventional method the reactions were optimized with respect to the parameters like i) solvents such as dioxin and tetrahydrofuran and dimethylformamide, ii) bases such as triethylamine and pyridine, iii) Molar ratio of acid chloride to substrates such as 1:1 and 2:1, and iv) reaction temperature which were room temperature and reflux temperature.

The structures of the final compounds were characterized by recording their Infra-red spectra on Jasco-FTIR spectrophotometer-410 and Nuclear magnetic resonance spectra on JNM-MY 60 FTNMR spectrometer and Varian ASM-100 spectrometer. Purity of all the synthesized compounds were confirmed with High performance liquid chromatography on TOSOH CCPM- II HPLC chromatograph, using Kingsorb C_{18} column, dimension 5 µm, 250 x 4.60 mm as stationary phase and Acetonitrile: methanol (60:40) as a mobile phase with the flow rate of 0. 5 ml/min.

Scheme II

Synthesis of N-acyl derivatives of heterocyclic substrates by microwave- assisted dry media method was carried out in two steps.

Step A: Synthesis of acid chlorides

Acid chlorides required for synthesis of N-acyl heterocycles by microwave- assisted dry media method were prepared by the same procedure, as in step A of scheme I.

Step B: Synthesis of N-acyl derivatives

A heterocyclic substrate (1.6 mmole), pyridine (0.48 mmole) and acid chloride (3.2 mmole) were impregnated individually, on basic alumina (1.6 gm), and were mixed thoroughly to obtain a free flowing powder in a porcelain dish. The reaction mixture was irradiated in a Samsung domestic microwave oven model no. G 2739N at 300 W for an appropriate time period as monitored by TLC. After cooling to room temperature the product was extracted with chloroform (3x15 ml) and was processed further to obtain the product as per the procedure mentioned in step B of scheme I.

Table 1 –Physical and elemental data of compounds

Compd	R	Mol. formula	m.p. (°C)	Found (%)(Calcd)				
				C	H	N	O	Cl
1_a	$C_5H_8NO_2$	$C_{11}H_{12}NO_2Cl$	76-77	58.53	5.36	6.20	14.18	15.70
1_b	$C_6H_{10}NO$	$C_{12}H_{14}NOCl$	225	64.41	6.31	6.26	7.15	15.85
1_c	$C_7H_4N_3O$	$C_{13}H_8N_3OCl$	135	60.59	3.13	16.30	6.21	13.76
1_d	$C_8H_5N_2O$	$C_{14}H_9N_2OCl$	120-121	65.50	3.53	10.91	6.23	13.81
1_e	$C_{23}H_{14}N_2O_4Cl$	$C_{29}H_{18}N_2O_4Cl_2$	146	65.82	3.42	5.29	12.1	13.40
1_f	$C_{12}H_{12}N_2O_2Cl$	$C_{18}H_{16}N_2O_2Cl_2$	250-251	59.51	4.44	7.71	8.80	20.07
1_g	$C_6H_{11}N_2O$	$C_{12}H_{15}N_2OCl$	175-176	60.37	6.33	11.73	6.70	14.85
1_h	C_5H_8NO	$C_{11}H_{12}NOCl$	166-167	63.00	5.77	6.68	7.63	16.90

Table 2 - Comparison between the conventional and the microwave-assisted method for the synthesis of N-acyl heterocycles.

Compound	Microwave irradiation		Conventional method	
	Yield (%)	Reaction Time (min)	Yield (%)	Reaction Time (hrs)
1_a	82	5	75	28**
1_b	74	3	69	22**
1_c	-	-	72	20*
1_d	-	-	35	14*
1_e	76	8	64	23**
1_f	72	2	62	13**
1_g	74	3.5	69	15**
1_h	61	1.5	52	2**

* = Reaction was carried out at room temperature in conventional synthesis.

** = Reaction was carried out at reflux temperature in conventional synthesis.

- = No product.

Compd	IR (cm^{-1}) (Neat)	^1H NMR (300 MHz, $CDCl_3$) (δ ppm)
1_a	2900 C-H ,1655 C=O, 1457 C=C,722 C-Cl	7.4 (m, 4H, Ar-H), 3.7 (s, 8H, 4xCH_2)
1_b	2946 C-H , 1649 C=O, 1596,1455 C=C, 722 C-Cl	7.3 (m, 4H, Ar-H), 3.45 (d, 4H, 2xCH_2), 1.6 (s, 6H, 3xCH_2)
1_c	2931 C-H , 1705 C=O , 1590,1457 C=C 722 C-Cl	7.8 (m, 8H, Ar-H)
1_d	2930 C-H , 1655 C=O, 1457 C=C , 722 C-Cl	7.75 (m, 8H, Ar-H), 1.25 (s, 1H, 1XCH)
1_e	2933 C-H , 1729 C=O, 1455 C=C, 722 C-Cl	7.3 (s, 18H, Ar-H)
1_f	2917 C-H , 1632 C=O, 1457 C=C, 722 C-Cl	7.4 (m, 8H, Ar-H), 3.6 (s, 8H, 4xCH_2)
1_g	2915, C-H , 1720 C=O , 1590,1458, C=C , 723 C-Cl	7.8 (m, 4H, Ar-H),1.295 (s, 3H, 1XCH_3), 1.295 (s, 8H, 4XCH_2)
1_h	2932, C-H , 1729 C=O ,1461 C=C , 722 C-Cl	7.24 (s, 4H, Ar-H), 1.569 (s, 8H, 4xCH_2)

Acknowledgments

Author thanks Dr. Kawishwar G.A Head, R &D, Centaur pharma, and Dr.Akamanchi, Pharmacy division, U.I.C.T for conducting NMR spectroscopy.

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Source of support: Nil, Conflict of interest: None Declared