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Selective-β-Acylation-of-2-Substituted Aromatic Heterocyclic Compounds.

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ABSTRACT

β-acylated hetero aromatic compounds were synthesized by Friedel Craft's acylation reacting 2-substituted aromatic heterocyclic molecules with acetic anhydride in presence of silica gel supported titanium chloride-TEBA[benzyl triethyl ammonium chloride] (SiO_2-$TiCl_4$-TEBA) at temperature 64-76^{0}C for the first time. The Catalyst was strongly surface supported by Silica Gel.

Keywords: Synthesis, Catalyst, Acylation, Selectivity.

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INTRODUCTION

The Friedel–Crafts acylation of aromatic molecules with acyl halides, which is an important process for the synthesis of perfumes, pharmaceuticals, fragrances, agrochemicals has been performed with at least a stoichiometric amount of Lewis acids [1-3]. This reaction is ubiquitous. Especially aromatic carbonyl compounds are very important intermediates for preparing fine chemicals in Pharma industries [4]. The most common experimental methods uses acid chlorides, which are usually prepared from the corresponding carboxylic acids, acetic anhydrides, thionyl chloride, as acylating agents and a stoichiometric or an excess amount of strong Lewis acids like $AlCl_3$, $TiCl_3$, $FeCl_3$ as a reaction catalyst [5,6]. This procedure suffers from severe and serious corrosion, waste problems and moisture sensitive [7]. Therefore, there are strong requirements for a keen alternative reaction which should be meeting our desire for environmentally benign chemical processes. Several new methods have been explored to overcome these demerits.

So that we need to develop a new catalyst system to obtain good products with quality and quantity. Acylation of aromatic heterocyclic compounds like thiophene, furan, pyrrole, pyridine was reported using different kinds of silica gel, zeolites, chlorides [8-17]. Thus, the results proved in earlier articles either fell short of goals for commercial reality or needed enhancement. We had developed the beta acylation of aromatic heterocycle compounds using acid anhydrides as acylating agents, SiO_2-$TiCl_4$-TEBA [benzyl triethyl ammonium chloride] as catalyst providing the use of stoichiometric amounts of the corrosive, toxic titanium chloride as a Friedel–Crafts reagent.

Experimental

All reagents and solvents used were of analytical grade and used without purification. The catalyst had prepared as follows

Preparation of the Catalyst $TiCl_4$–SiO_2–TEBA (Complex):

To a solution of TEBA (3.28 g, 0.2 mol) and dry dichloromethane (10 mL) was slowly added titanium tetra chloride (11g, 0.4 mol),silica gel-GF-254 (11g) at 0-5 ^{0}C in a conical flask under nitrogen atmosphere. At the end of this exothermic reaction, filtration gave a pure pale yellow crystal, which was washed with dry dichloromethane/diethyl ether , and dried in vacuum to give the desired catalyst for the acylation on 2-Substituted heterocyclic compounds.

Typical Procedures:

β- Acylated hetero aromatic compounds.

A mixture of furan-2-carboxylic acid methyl ester (48 mmol, 3.8 g), acetic anhydride (15 mmol, 1.10 g) and catalyst $TiCl_4$-SiO_2-TEBA (0.5 g) was stirred at temperature 64 -76^{0}C under the nitrogen atmosphere and monitored by GC Mass. After completion of the reaction 70 ml

water added to the product and then organic layer was purified with 10% of $NaHCO_3$ Solution and distilled under high vaccum pressure. Light green colour liquid was obtained. This procedure was repeated for the corresponding heterocyclic compounds such as 2-substituted pyridine, 2-substituted pyrrole, 2-substituted thiophene.

Analytical Data: (see table-1for the compounds 2a, 2f, 2j, 2n)

[2a] 4-Acetyl-2-nitro thiophene: ^{1}HNMR ($CDCl_3$) δ. 2.5 (s, $COCH_3$), 7.1 (s, ArH), 7.6 (s, ArH). IR (cm^{-1}) 1601, 1660, 1470 cm^{-1}. Mass (m/z) 102,171,218

[2f] 4-Acetyl furan-2-carboxylic acid methyl ester: ^{1}HNMR ($CDCl_3$) δ. 2.5 (s, $COCH_3$), 3.8 (s, $COOCH_3$), 7.5 (ArH), 7.7 (s, ArH). IR (cm^{-1}) 1721, 1665 1405, 2954, 3017 cm^{-1}. Mass (m/z) 127,168,149

[2j] 4-Acetyl 1H pyrrole-2-carboxylic acid: ^{1}HNMR ($CDCl_3$) δ. 11.9(s, COOH brs), 2.6(s, 3H) 5.6-6.0(ArNH,d) , 7.6 (ArH), 7.85 (ArH,d). IR (cm^{-1}) 1849,1667,1528,2617 cm^{-1}. Mass (m/z) 149, 153,190

[2n] 4-acetyl-pyridine-2-carboxylic acid: ^{1}HNMR ($CDCl_3$) δ11.8 (s, brs, COOH), 2.5 (s, 3H) 7.8 (s, ArH), 7.5 (ArH, d), 8.0 (NCH, d). Mass (m/z) 150, 154, 165

RESULTS AND DISCUSSION

The acetylation of heterocycle molecules were carried out by using $TiCl_4$–SiO_2–TEBA has showed higher activity. Five and six membered hetero aromatic rings were selectively acylated by using this catalyst as first time at possible handling temperature conditions. Using this efficient catalyst system, conversion of the acylation is observed at 63-96 %. The acetylation of the heteroaromatic compounds is highly selective at β–position of the ring with this silica supported $TiCl_4$-TEBA catalyst to yield the bulkier product. No by products were formed in reactions. The conversion has been increased with the decrease of selectivity in most reaction cases. The low selectivity has been ascribed to the kinetic effect. The $TiCl_4$-TEBA was promoted the reaction at active stage by the addition of external surface area of silica gel. Products were found to be in pure form. Good homogeneous nature was obtained by the $TiCl_4$-TEBA due to additional support of silica gel.

The analytical data on compounds 2a, 2f, 2j, 2n confirm product formations. In proton NMR (Solvent-$CDCl_3$) , the two aromatic protons such as 3,5 positions in the five membered rings were shown their δ signals as singlets at low and high regions respectively (compounds 2a, 2f, 2j) where as six membered heterocycle was shown its aromatic proton δ signal at 7.8 , 7.5 , 8.0. The formed basic acyl group showed its delta value of methyl at 2.5 or 2.6. The NH peak of substituted pyrrole moiety in ^{1}HNMR showed at 5.6-6.0 as doublet. Substituted Pyridine showed its delta values of proton NMR at 11.8 (-COOH), 7.8 (3rd position-High value due to hindered place of two e^- withdrawing groups), 7.5 (4th position-Low value due to only one withdrawing group to its adjacent), 8.0 (5th position due to adjacent to nitrogen atom in

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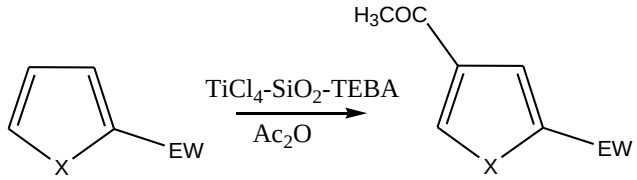
pyridine) .Compounds 2a, 2f, 2j had showed their IR (KBr) values of carbonyl function at 1660-1661 , 1665, 1667 cm^{-1} respectively.2f had showed its ester stretching at 1721 cm^{-1} in its IR data where as 2j showed its carboxylic group IR stretching at 1849 cm^{-1}. Mass (m/z) values of 2a, 2f, 2j, 2n showed at 102,127,149, 150 respectively.

Here with reporting, that it may be stated as in the acetylation of aromatic heterocyclic molecules on $TiCl_4$–SiO_2–TEBA and it is the Lewis acidity of the catalyst that brings about the reaction, physical, electronic factors which largely determine the direction of the β–substitution (Scheme-1) based on research work reported by RA Benkeser [18].



1a, 1b, 1c, 1d (**1-14**) **Scheme-1** 2a, 2b, 2c, 2d (**2a-n**)

EW=Electron withdrawing group. X=S Thiophene 1a, X=O Furan 1b, X=NH Pyrrole 1c, X = N Pyridine 1d

Table 1 .Selective β-acylation of 2-substituted aromatic heterocyclic compounds (scheme -1).

S.No	X	Type of Heterocyclic compound	EW	Temp (^0C)	Time (h)	Conversion (%)	Selectivity, β-acylation
1a (1)	S	Thiophene	$-NO_2$ (2a)	65	4	88	95
1a (2)	S	Thiophene	$-COCH_3$ (2b)	67	3	92	94
1a (3)	S	Thiophene	-COOEt (2c)	70	5	94	97
1a (4)	S	Thiophene	-CHO (2d)	68	4	96	93
1b (5)	O	Furan	-Br (2e)	66	5	96	92
1b (6)	O	Furan	$COOCH_3$ (2f)	64	4	91	95
1b (7)	O	Furan	$-COCH_3$ (2g)	71	5	89	96
1b (8)	O	Furan	-CHO (2h)	67	6	90	98
1c (9)	NH	Pyrrole	-Cl (2i)	68	5	92	90
1c(10)	NH	Pyrrole	-COOH (2j)	69	4	90	94
1c(11)	NH	Pyrrole	-CHO (2k)	70	5	88	96
1c(12)	NH	Pyrrole	$-COCH_3$ (2l)	70	4	90	92
1d(13)	N	Pyridine	$-NO_2$ (2m)	76	6	68	90
1d(14)	N	Pyridine	-COOH (2n)	67	4	63	89

CONCLUSIONS

The silica supported $TiCl_4$-TEBA offers a more efficient and selective acylation method for extremely pure isolated isomers by using Ac_2O, those which should be used as an intermediates for the preparation of synthetic drugs. This catalyst was reported first time and which does not producing waste products in the reactions unlike Lewis acids and its corresponding acids. Catalyst was prepared easily in our research laboratories and of low price.

This methodology is ecofriendly.The further developments of this reaction were under investigation

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REFERENCES

[1] House HO. Modern Synthetic Reactions, 2nd ed.; W.A.Benjamin: California, 1972, pp 797:819.
[2] Olah GA. Friedel–Crafts Chemistry; John Wiley & Sons: New York, 1973.
[3] Chiche B, Finiels A, Gauthier C, Geneste PJ. Org Chem 1986; 51;2128–2130.
[4] U Viplavaprasad, M Brahmayya, D Samsonu, K Vijayakumar, MV Raghupathiraju. Sci. Revs. & Chem. Communs. 2011; 1(1): 58-62.
[5] Heaney H. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford,1991; Vol. 2, pp 733–752.
[6] M Brahmayya, B Venkateswararao, D Krishnarao, S Durgarao, U Viplava Prasad, T Damodharam, R Mishra. J Pharm Res 2013; 7(6): 516-519.
[7] R Levine, JV Heid, MW Farrar. J Am Chem Soc 1949; 71 (4): 1207–1209.
[8] F Richard, J Drouillard, H Carreyre, JL Lemberton G. Pérot. Studies in Surface Sci. and Cat 1993:78:601–606.
[9] WF Hoeldrich. Stud Surf Catal 1989; 49: 69.
[10] AR Katritzky, S Kazuyuki, SK Singh. Croatica Chemical Acta 2004; 77(1-2): 175-178.
[11] KP Boroujeni. Turk J Chem, 2010; 34: 621-630.
[12] AV Rao, V Veeraiah, AVP Rao, BK Babu, M Brahmayya, Res O Chem Int 2014; 40(2): 1532.
[13] HJ Anderson, ChE Loader, A Foster. Can J Chem 1980; 58: 2527.
[14] P Ramreddy, M Subrahmanyam, SJ Kulakarni. Catalysis Lett 1998; 54: 95-100.
[15] UV Prasad, M Brahmayya and M Syambabu. Int J Chem Sci 2011; 9(1): 371-377.
[16] Kirth-Othmer ,Encyclopedia of chemical technology (4th Edition),vol-20 (pyridine and pyridine derivatives)
[17] M Brahmayya, ML Wang. Int J Chem 2014; 35:1522-1530.
[18] RA Benkeser, RB Currie. J Am Chem Soc 1948; 70: 1780-1782.