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Catalytic Trans N-acylation of Anilides with α-Chloropropionyl Chloride over Zeolites⁺

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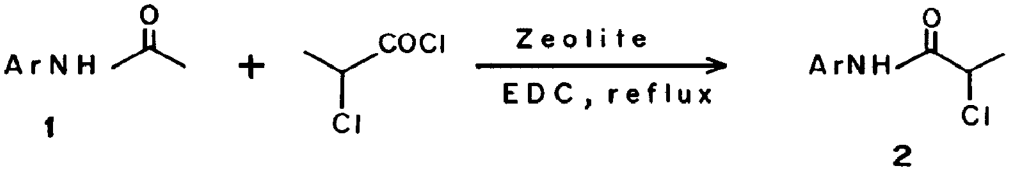
***Abstract** : A mild and effective method of zeolite catalyzed trans N-acylation of anilides in liquid-phase is described.*

Trans N-acylation, in which one amide function is directly converted into another, finds widespread application both in amino sugars, viz. 2-amino-2-deoxy sugars of polysaccharides, offering starting points for specific degradations[1] and in penicillin and cephalosporin derivatives, affording new class of β-lactam antibiotics.[2] Moreover, reversible acyl transfer reactions catalyzed by enzymes such as lipase in organic solvent have great practical utility, in addition to being of theoretical interest, in asymmetric synthesis due to their facile recognition.[3] A few methods of trans N-acylation with either acids or anhydrides have, however, been reported using highly acidic catalysts such as trifluoroacetic acid - trifluoroacetic anhydride,[4] TFAA-DBN,[2] and $AlCl_3$[5] and most of them are non-catalytic. Of late, increasing attention has been paid to the synthesis[6] and synthetic applications of α-chloroanilides bearing aromatic substituents particularly in the synthesis of agrochemicals (as herbicides).[7]

Zeolites and other molecular seives are known to display unique catalytic properties in diverse areas.[8] In view of the practical utility and mechanistic interest of trans N-acylation of amides, we wish to report, for the first time, a new catalytic method for trans N-acylation of acetanilides with α-chloropropionyl chloride catalyzed by zeolites (Scheme 1).



Scheme–1

HZSM-5[9], ALPO-11[10], Zr-ZSM-5[11], VAPO-5[12] and TS-1[13] were prepared following literature procedure. In a typical reaction, a mixture of acetanilide (1.35 g; 10 mmol), α-chloropropionyl chloride (1.4 g; 11 mmol) and zeolite (100 mg) in dichloroethane (30 ml) was refluxed for 5 h. The products were analyzed by GLC, purified by flash chromatography and well characterized.[14] The results are summarized in Tables 1 and 2.

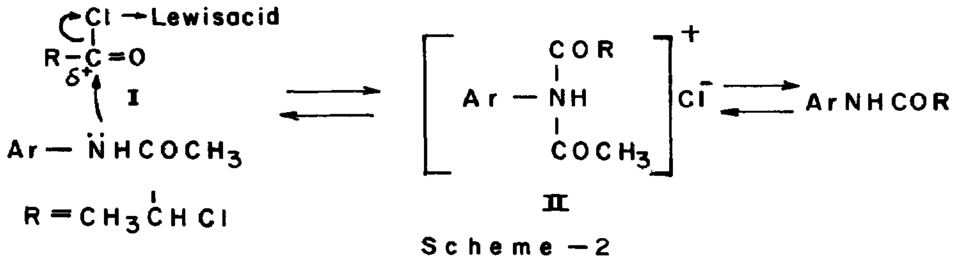
Table 1 : Zeolite catalyzed transacylation of acetanilide with α-chloropropionyl chloride :

Entry	Zeolite	Product, 2 Yield (%)[a]
1	No catalyst	20
2	H-ZSM-5	60
3	4A	58
4	TS-1	56
5	ALPO-11	50
6	VAPO-5	42
7	Zr-ZSM-5	32

a Determined by GLC; Column SE-30 (10%) temperature 160°C; the rest is essentially unreacted acetanilide

Evidently, HZSM-5 has exhibited better catalytic activity compared to other zeolites screened, owing to the presence of both Lewis and Bronsted acid sites in it. Surprisingly, even the oxidation catalysts such as VAPO-5 and TS-1 could catalyse the reaction as effectively as HZSM-5 to produce the transacylated products. In order to gauge the scope and generality, we have subjected a variety of substituted acetanilides for the trans N-acylation reactions. It may be mentioned that, while the 4-nitro (entry F) reacted moderately to give the required product, the 2-nitro (entry H) failed to undergo the trans-N-acylation (Table 2).

Mechanistically, it may be presumed that Lewis acid sites Al^{3+} and Ti^{4+} present on the surface of H-ZSM-5 and TS-1 respectively, can activate the acid chloride by way of coordination, thereby increasing the electrophilicity of the carbonyl carbon to generate the stabilized acylinium cation (I) which in turn attacks the nitrogen of the amide preferentially to form the diacylated product (II) which in turn equilibrates between the acetanilides leading to formation of the transacylated product (Scheme 2). Further work is in progress to improve the selectivity of the process in obtaining mostly the trans product and its potential in generating other types of amides.



Scheme −2

Table 2 : Trans N-acylation of acetanilides with α-chloropropionyl chloride catalyzed by H-ZSM-5

Entry	Substrates, 1 R	Product, 2 Yield (%)[a]	m.p. (lit)[b,6] °C
A	H	53	82-83 (82)
B	4-Methyl	58	115 (115-116)
C	4-Methoxy	49	101-2 (101-2)
D	4-Chloro	41[c]	112-114 (112)
E	4-Bromo	55	122-125 (124)
F	4-Nitro	30	134 (134-135)
G	2-Fluoro	31[c]	74-76 (74-76)
H	2-Nitro	No reaction	
I	Cyclohexyl	15[d]	104 (105)

a Isolated after column chromatographic purification (SiO_2)

b Number in parenthesis refers to melting point reported in the literature (see ref.6)

c No products formed in the absence of catalyst

d The remainder is tarry material

In conclusion, the results described herein demonstrate the novely of zeolites in exercising unique transformation of trans N-acylation of anilides, thus contributing to environment-friendly method of producing α-chloroanilides.

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14 Products 2 were characterized by IR ^{1}H and ^{13}C NMR and MS Analyses. ^{13}C NMR values for selected compounds : *For 2C* : ^{13}C NMR (200 MHz; $CDCl_3$) : δ 22.6 (CH_3), 55.6 (OMe), 56.1 (CH), 114.3 (C and C), 122.2 C_2 and C_6 (C_3 and C_5), 130.2 (C_1), 157.1 (C_4) and 167.7 (C=O). *For 2G* : ^{13}C NMR (200 MHz; $CDCl_3$) : δ 22.7 (CH_3), 56.2 (CH) 115.0 and 115.3 (C_4 and C_5), 121.8, 124.7, 124.8, 150.6 (C-F) and 167.7 (C=O).

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