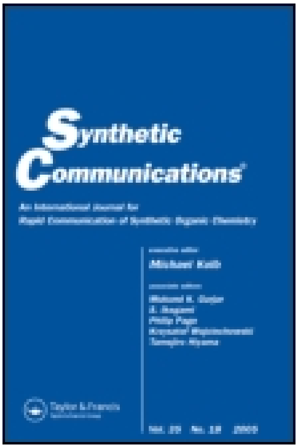

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SIMPLE, HIGH YIELD PREPARATION OF *N*-BENZYLACETAMIDES BY LEWIS ACID-CATALYSED REACTION OF BENZYL CHLORIDES OR BENZYL METHYL ETHERS WITH ACETONITRILE

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ABSTRACT: Reaction of either benzyl chlorides or benzyl methyl ethers with *hydrated* ferric chloride in acetonitrile results in smooth Ritter reaction and formation of *N*-benzylacetamides in excellent yield.

The Ritter reaction is a well established and extensively used method for the preparation of a wide range of amides, lactams and other heterocycles.[1,2] The classical experimental procedure involves treatment of an alcohol or alkene with a strong protic acid, most usually 85-90% sulfuric acid, and trapping of the carbenium ion thus formed by a nitrile, followed by hydrolysis of the nitrilium ion. Yields are often excellent in spite of the apparent harsh conditions and the possibilities for multiple reaction pathways in an overall conversion which proceeds through two high energy, formally charged intermediates.

In connection with other work we required a series of *N*-benzylacetamides, $ArCH_2NHCOCH_3$, in which Ar was electron rich, and considered accessing these through Ritter reaction of the benzyl alcohols $ArCH_2OH$. There are, surprisingly,

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TABLE 1

Preparation of *N*-benzylacetamides $ArCH_2NHCOCH_3$ by reaction of $ArCH_2Cl$ with CH_3CN and a Lewis acid catalyst

Ar[a]	Catalyst[b]	Time, h	Yield, %
C_6H_5	$AlCl_3$	12	70[d]
2-$CH_3C_6H_4$	$FeCl_3$	0.5	54[e]
			78[d]
3-$CH_3C_6H_4$	$FeCl_3$	0.5	46[e]
4-$CH_3C_6H_4$	$FeCl_3$	0.5	70[e]
4-t-BuC_6H_4	$FeCl_3$	0.5	71[e]
2,5-$(CH_3)_2C_6H_3$	$FeCl_3$	0.5	78[e]
	$SnCl_4$	1	62[d]
3,4-$(CH_3)_2C_6H_3$	$FeCl_3$	0.5	69[e]
2,4,6-$(CH_3)_3C_6H_2$	$FeCl_3$	0.5	71[e]
2,6-$(CH_3)_2$-4-t-BuC_6H_2	$FeCl_3$	0.5	80[e]
	$AlCl_3$	10	84[d]

[a] 10 mmol. [b] 40 mmol. [c] Refers to pure, isolated products.
[d] Reflux temperature. [e] Room temperature.

rather few examples of amide preparation from Ritter reactions of simple benzyl alcohols, and almost all of these involve the sulfuric acid approach. For our study, however, we were concerned that ring sulfonation and/or proto-de-t-butylation might lead to complications with certain substrates and hence a simple and practical variation on the classical Ritter reaction was sought.

We examined first the reactions of a number of benzyl chlorides with Friedel-Crafts catalysts in acetonitrile, and the results are summarised in Table 1. In terms of yields, these were generally satisfactory, and certainly comparable with the data available for classical Ritter reactions with $ArCH_2OH$. Of the catalysts examined, ferric chloride was best in terms of overall cleanness. Even so, formation of highly coloured byproducts was observed in virtually every reaction, probably indicative of alternative pathways to the Ritter process for either $Ar\overset{+}{C}H_2$

TABLE 2

Preparation of *N*-benzylacetamides $ArCH_2NHCOCH_3$ by reaction of $ArCH_2Cl$ or $ArCH_2OCH_3$ with CH_3CN and $FeCl_3 \cdot 6H_2O$[a]

$ArCH_2X$			
Ar	X	Time, h	Yield, %[b]
C_6H_5	Cl	16	74
	OCH_3	144	22
$2\text{-}CH_3C_6H_4$	Cl	6	98
	OCH_3	48	70
$3\text{-}CH_3C_6H_4$	Cl	12	92
	OCH_3	72	22
$4\text{-}CH_3C_6H_4$	Cl	6	96
	OCH_3	18	96
$4\text{-}t\text{-}BuC_6H_4$	Cl	5	98
	OCH_3	16	97
$2,5\text{-}(CH_3)_2C_6H_3$	Cl	6	94
	OCH_3	36	98
$3,4\text{-}(CH_3)_2C_6H_3$	Cl	6	97
	OCH_3	36	97
$2,4,6\text{-}(CH_3)_3C_6H_2$	Cl	5	96
	OCH_3	16	96
$2,6\text{-}(CH_3)_2\text{-}4\text{-}t\text{-}BuC_6H_2$	Cl	5	98
	OCH_3	14	96

[a] For details, see Experimental. [b] Refers to pure, isolated products.

and/or $ArCH_2\overset{+}{N}{\equiv}CCH_3$. All of the reactions had been carried out with anhydrous Lewis acid catalysts and carefully dried acetonitrile.

We then considered the possibility of minimising byproduct formation by *in situ* trapping of the nitrilium ion by water, and this proved to be remarkably straightforward. Thus, use of *hydrated* ferric chloride, $FeCl_3 \cdot 6H_2O$, as catalyst instead of anhydrous $FeCl_3$ resulted in smooth, clean reaction and formation of the *N*-benzylacetamides in excellent yield. Either benzyl halides or benzyl methyl ethers could be used as carbenium ion sources and the experimental results are summarised in Table 2. The reactions with the benzyl ethers were significantly slower than those with the benzyl chlorides and in the cases of methyl benzyl ether and methyl 3-methylbenzyl ether low yields of amides were obtained.

These results represent a useful extension to the superficially investigated and little utilised classical Ritter reactions of benzyl alcohols. The concept of *in situ* hydrolysis of nitrilium ion intermediates by use of hydrated Lewis acid catalysts may prove beneficial in other Lewis acid mediated Ritter reactions.

EXPERIMENTAL

General procedure for preparation of N-benzylacetamides:- A solution of either the benzyl chloride or the benzyl methyl ether (10 mmol) in acetonitrile (25 ml) was added dropwise during 15 min to a stirred solution of ferric chloride hexahydrate (10.8 g, 40 mmol) in acetonitrile (25 ml) at room temperature. When addition was complete the mixture was stirred and heated under reflux for the appropriate time (Table 2; reactions were monitored by tlc). The cooled reaction mixture was then poured on to crushed ice (15 g) and 2N HCl (15 ml) and ether (15 ml) were added. The organic phase was separated, washed with 2N HCl (15 ml), water (15 ml) and satd. NaCl solution (15 ml). It was then dried ($MgSO_4$), filtered, and the filtrate evaporated under reduced pressure to give the crude product. All of the amides thus prepared are known compounds and the crude products were purified by crystallisation. The pure products were compared (mp, mmp, ir, ^1H nmr) with genuine samples prepared independently.

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