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N-ALKYLATION OF AMIDES AND N-HETEROCYCLES WITH POTASSIUM FLUORIDE ON ALUMINA

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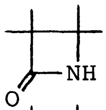
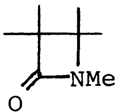
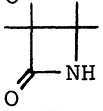
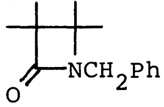
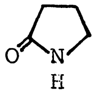
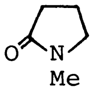
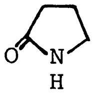
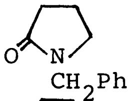
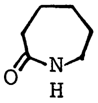
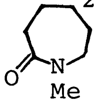
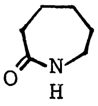
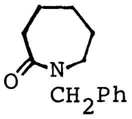
Alumina coated with potassium fluoride promotes smooth N-alkylation of carboxamides, lactams, and other N-heterocycles with alkyl halides or dialkyl sulfate under mild conditions.

N-Alkylation of carboxamides is not only important for the selective synthesis of secondary and tertiary amines,1) but also essential for the preparation of a number of pharmaceuticals.2) However, the presence of two potentially nucleophilic sites, oxygen and nitrogen atoms, complicates the reaction; the site of alkylation varies depending on the reaction conditions used. Furthermore, conventional methods of N-alkylation require rather drastic conditions using strong bases, e. g., sodium, sodium amide, sodium hydride, potassium tert-butoxide, etc., and are apt to give impure products in relatively low yields.3)

Recently, phase-transfer-catalyzed reactions and heterogeneous reactions were reported to be excellent alternatives to the conventional methods; aqueous sodium hydroxide-benzene-catalyst and solid sodium hydroxide-potassium carbonate-benzene-catalyst are typical examples of the former, and solid potassium hydroxide in dimethylsulfoxide is one of the latter.4-8)

On the other hand, there has been increasing use of inorganic solid supports as reagents or reaction media in recent years.9) In the previous papers from our laboratory, we reported that alumina coated with potassium fluoride (KF-alumina) was effective in promoting various types of alkylations and was even applicable to the synthesis of crown ethers.10) In the present paper, we report a convenient method of preparing N-alkylated amides and related

Table 1. N-Alkylation of amides and lactams with KF-alumina[a]

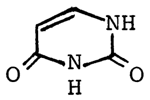
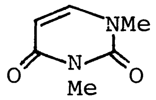
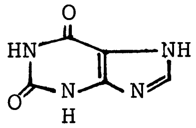
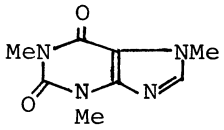
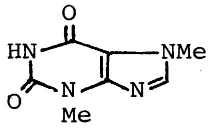
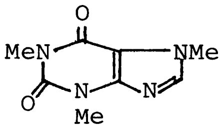
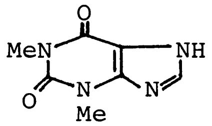
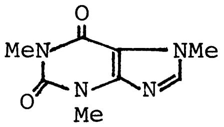
Substrate	Halide	Time/h	Product	Yield/%[b]
HCONHPh	MeI	2[c]	HCON(Me)Ph	83
MeCONHPh	MeI	6[d]	MeCON(Me)Ph	93
MeCONHPh	$PhCH_2Cl$	24[d]	$MeCON(Ph)CH_2Ph$	82
$MeCONHCH_2Ph$	MeI	72	$MeCON(Me)CH_2Ph$	85
$PhCONH_2$	MeI	48[d]	$PhCON(Me)_2$	75[e]
PhCONHPh	MeI	24	PhCON(Me)Ph	90
	MeI	3		100[f]
	$PhCH_2Cl$	72		83
	MeI	5		86[f]
	$PhCH_2Cl$	48		81
	MeI	24		73[f]
	$PhCH_2Cl$	72		61

a) Unless otherwise mentioned, reaction was carried out in 1,2-dimethoxyethane at room temperature. b) Isolated yields after purification unless otherwise noted. c) at 0 °C. d) Acetonitrile was used as a solvent. e) PhCONHMe (0.5 %) was detected. f) GLC yields determined by use of internal standards. A column packed with PEG 20M on Chromorb W NAW was used.

substances with KF-alumina.

The reaction of an amide was usually carried out with an alkyl halide (1.2-1.5 equiv) in the presence of KF-alumina[11] (ca. 2.5 equiv) in acetonitrile or 1,2-dimethoxyethane with stirring at room temperature. By taking advantage of the solid-liquid two phase reaction, a product was easily isolated with simple and non-aqueous work-up, i. e., filtration of inorganics, evaporation of the solvent, and, when necessary, purification by distillation or recrystallization.

Table 2. N-Methylation of uracil and xanthine derivatives[a)]

Substrate	Time/h	Product	Yield/%[b)]
	18		89
	24		61
	24		92
	24		88

a) Reaction of a substrate (1 mmol) with dimethyl sulfate (1 mmol) and KF-alumina (0.75 g, KF 5 mmol) was carried out in acetonitrile (10 ml) at room temperature.
b) Isolated yields after preparative TLC developed in chloroform-ethanol (4:1).

Thus, various aliphatic and aromatic carboxamides were alkylated at the nitrogen in excellent yields. Typical examples are summarized in Table 1. Although a fairly long reaction time was required in some cases, all the reactions were completed without heating. Products obtained were quite pure in most cases and none of the O-alkylated product was detected. N-Methylation of formanilide with methyl iodide went to completion within a short reaction time at 0 °C; partial decomposition of the starting material was observed when the reaction was carried out at room temperature. The reaction of benzamide with three moles of methyl iodide gave the N,N-dimethylated product. Attempt to isolate the monomethylated amide were unsuccessful.

In addition to simple acyclic carboxamides, cyclic amides of various ring sizes, i. e., β-, γ-, and ε-lactams, were easily alkylated in excellent yields (Table 1). The reaction of a β-lactam with benzyl chloride proceeded smoothly without any side reaction.

Alkylation of nucleic acid components has been the subject of deep interest in recent years.[12)] Ogilvie and his coworkers have reported that tetrabutylammonium fluoride promotes rapid alkylation of purines, pyrimidines, nucleosides, and nucleotides.[13)] KF-Alumina was also found to be effective for N-methylation of these bases. Uracil and xanthine derivatives reacted with dimethyl sulfate at room temperature to give N-methylated products in good isolated yields (Table 2). No special selectivity of the position of alkylation was observed for these bases. Thus, xanthine was permethylated to afford caffeine. A simillar observation was also reported in the case of tetrabutylammonium fluoride.[13)]

In conclusion, KF-alumina is an effective reagent for N-alkylation of carboxamides, lactams, and other N-heterocycles. Although it is not so reactive as tetraalkylammonium fluoride, it is superior in terms of ease of handling and economy.

References

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11) We used KF-alumina of Type B prepared as described previously.[10)]

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