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AN IMPROVED MODIFICATION OF RITTER REACTION

A. García Martínez*[a], R. Martínez Alvarez[a], E. Teso Vilar[a],
A. García Fraile[a], M. Hanack*[b], L.R. Subramanian[b]

[a]Departamento de Química Orgánica, Facultad de Ciencias Químicas,
Universidad Complutense, E-28040 Madrid, Spain

[b]Universität Tübingen, Institut für Organische Chemie,
Lehrstuhl Organische Chemie II,
Auf der Morgenstelle 18, D-7400 Tübingen 1, Federal Republic of Germany

Summary: The reaction of alcohols 1 with trifluoromethane sulfonic anhydride (Tf_2O) in dichloromethane in presence of a 2:1 excess of nitriles 3 affords the corresponding amides 5 in good yields.

The reaction of alcohols with nitriles in concentrated sulfuric acid (Ritter reaction) has been proved to be a good method for the preparation of primary and secundary amines via the hydrolysis or reduction of the initially formed amides[1]. The Ritter reaction has the disadvantage that it functions well (50-90% yield) only in the case of tertiary alcohols 1 (R^1, R^2, $R^3 \neq H$). Thus the yields of the amides are low in the case of secondary alcohols, while no reaction takes place with primary alcohols[2,3]. We have now found that primary as well as secondary (and tertiary) alcohols 1 react with nitriles 3 in the presence of triflic anhydride to give amides 5 in good yield (Table). The reaction is carried out by adding a dichloromethane (20 ml) solution of the alcohol 1 (10 mmol) to a mixture of anhydride (10 mmol) and nitrile 3 (20 mmol) in dichloromethane (20 ml) followed by hydrolysis with saturated $NaHCO_3$ solution. In contrast to the normal Ritter reaction the best yields of the amides are obtained starting from primary and secondary alcohols, thereby extending the possibilities of Ritter reaction. Advantages of our method are also the mild reaction conditions and easy workup. Therefore, our method is a convenient alternative to the reaction of chlorodiphenylmethylium hexachlorantimoniate with alcohols in nitrile solvents[4].

It has been reported that methyl-[5,6] and benzyl triflate[7] react with nitriles to form the corresponding nitrilium salt. Therefore, we presume that the reaction of 1, Tf_2O and the nitrile 3 proceed via a N-alkylation of 3 by the first formed alkyltriflate 2 with the formation of nitrilium salts 4.

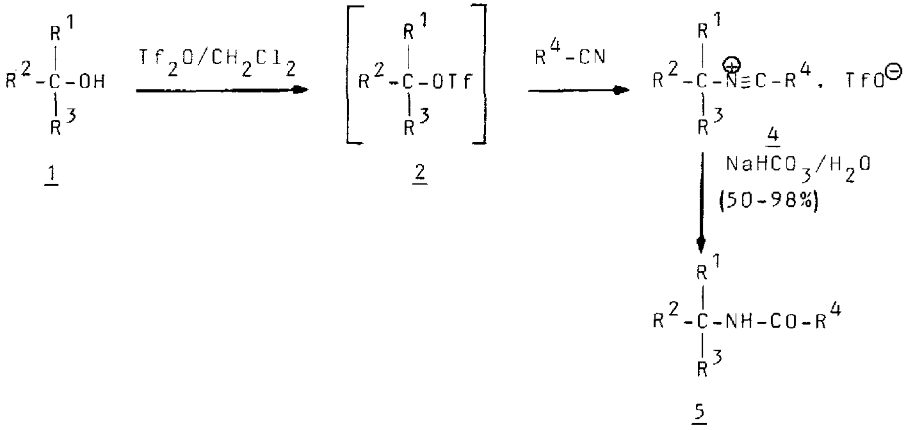

Table. Preparation of Amides 5

R^1	R^2	R^3	R^4	Temp.(°C)	Time (h)	Yield (%)	mp (°C) or bp (°C)/torr
H	H	C_6H_5	CH_3	RT	5	87	59-60
H	H	C_6H_5	t-C_4H_9	RT	5	75	76-78
H	H	n-C_4H_9	CH_3	RT	5	90	90-92/1.5
H	H	CH_3	C_6H_5	RT	5	82	68-70
H	-C_6H_{12}-		CH_3	-20	2	75	102-103
H	CH_3	CH_3	C_6H_5	-20	2	68	103-104
CH_3	CH_3	CH_3	CH_3	-20	2	50	98-99
1-Adamantyl			CH_3	RT	2	98	148-149

Our method is generally applicable, because it avoids the separate preparation of the often unstable alkyl triflates[8], and makes possible the direct use of primary and secondary alcohols in the Ritter reaction. The comparatively low yield from tertiary alcohols is probably due to the competing elimination reaction of the unstable intermediate triflate.

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