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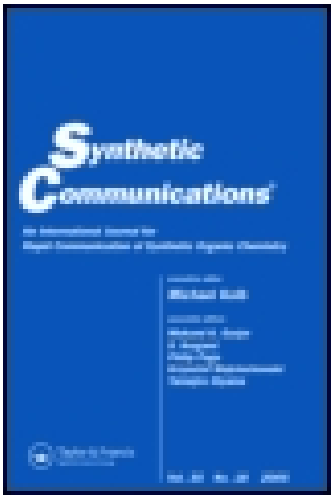

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N-Alkylated 2-Trifluoromethyl-4-quinolones by Addition of Base and an Alkylating Agent to 2-Trifluoroacetylaminoacetophenone

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N-ALKYLATED 2-TRIFLUOROMETHYL-4-QUINOLONES BY ADDITION OF BASE AND AN ALKYLATING AGENT TO 2-TRIFLUOROACETYLAMINOACETOPHENONES.

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2-Trifluoroacetylaminoacetophenones **1** are cyclized to N-alkyl-2-trifluoromethyl-4-quinolones **2** in one pot with concomitant N-alkylation in 40 to 74% yield using potassium hydroxide in acetone containing an alkylating agent.

The growing importance of the quinolone antibiotics has led to increased interest in the synthesis of 4-quinolones[1]. We report here an efficient two step-one pot construction of this functionallized heterocyclic system from readily available precursors.

The procedure of Johnstone[2] (TFAA then MeI/acetone/KOH) is an effective method for the preparation of alkylated aromatic amines. However, treatment of N-acylated 2-aminoacetophenones with base causes cyclization to 2-, and /or 4-quinolones as described by Camps[3]. In cases where the amide carbonyl does not have α-hydrogens there is only one product formed. This product results from abstraction of a

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proton α to the ketone followed by attack of this anion on the amide carbonyl with loss of water to give a 4-quinolone. We have found that the presence of an alkylating agent during the Camps reaction accomplishes both transformations in one pot. A good alkylating agent is required for this transformation. Methyl iodide, ethyl iodide, and benzyl bromide were all acceptable, but in one experiment ethyl bromide was not reactive enough.

To verify the regiochemistry of the alkylation step, the same transformation was carried out in a stepwise fashion by first alkylating 4,5-dimethoxy-2-aminoacetophenone with dimethyl sulfate and potassium carbonate in acetone. After separation of the desired monomethyl amine from the dimethyl product and starting material, the N-methylated cyclization substrate (**1f**) was formed by acylation with trifluoroacetic anhydride.[4] This compound is, presumably, the intermediate formed from (**1d**) in the first step of the alkylation-cyclization sequence. Compound (**1f**) smoothly underwent cyclization to 6,7-dimethoxy-1-methyl-2-trifluoromethyl-4-quinolone (**2d**) in 64% yield under the same basic conditions as (**1d**) but without an alkylating agent.

This reaction provides a quick route to 2-trifluoromethyl-4-quinolones alkylated on the nitrogen atom with a variety of alkyl groups and displays tolerance for a wide variety of functional groups on the phenyl ring. By contrast, the method of Bajwa and Joullie[5], for example, gives mixtures of regioisomers which are unsubstituted at Nitrogen.

General Procedure

A solution of trifluoroacetylaminoacetophenone[4] in dry acetone was treated with a 5-fold excess of alkylating agent followed by a 4-fold

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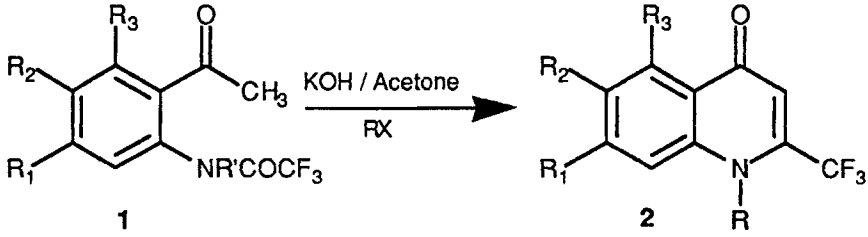
Table. N-Alkyl-2-trifluoromethyl-4-quinolones



1[4]	R1	R2	R3	R'	RX	2[a]	Yield %	mp (°C)
a	H	H	H	H	MeI	**a**	74	137-139
b	H	Cl	H	H	MeI	**b**	63	161-163
c	H	OMe	OMe	H	MeI	**c**	54	118-124
d	OMe	OMe	H	H	MeI	**d**	49	258-259
e	H	$N(CH_2CH_2)_2O$	H	H	MeI	**e**	53	212-215
d	OMe	OMe	H	H	EtI	**f**	40	162-165
d	OMe	OMe	H	H	BnBr	**g**	44	158-160
f	OMe	OMe	H	Me	none	**d**	64	258-259

a All compounds are analytically pure (C,H,N) and have NMR and IR data consistent with the assigned structures.

excess of dry powdered potassium hydroxide. The mixture was stirred under nitrogen and heated at reflux for 3 to 18 h. The acetone was removed at reduced pressure and the residue triturated with water giving a crystalline compound. Optionally, extraction of the aqueous slurry with dichloromethane, drying the organic layer over sodium sulfate, and removal of the solvent followed by recrystallization or chromatography gave the product.

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2. Johnstone, R. A. W., Payling,D. W., and Thomas, C. ,J. Chem. Soc (C) 1969, 2223.

3. Camps, R. Chem. Ber., 1899, 3228; See also Jones, G. in Katritsky and Ree's Comprehensive Heterocyclic Chemistry vol 2 page 418-9 Pergamon Press, NY 1984.

4. All of the trifluoroacetylaminoacetophenones were prepared by dissolving the appropriate aniline in excess trifluoroacetic anhydride at 10°C and warming to room temperature. The solvent was evaporated and the residue recrystallized from ethanol or ether.

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