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TRIFLAMIDES FOR PROTECTION AND MONOALKYLATION OF AMINES AND A NEW GABRIEL SYNTHESIS.

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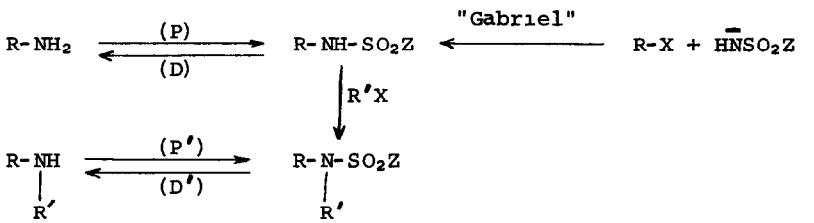
The interrelated synthetic problems surrounding the protection, deprotection, and monoalkylation of amines were explored in an earlier communication,[1] using the phenacylsulfonyl group for protection and zinc reduction for its removal. The phenacylsulfonamide derivatives, furthermore, could be smoothly monoalkylated so that net monoalkylation of the amines was realized on removal of the protecting group. The general schema is reproduced in equation (1) with the addendum of a parallel for the Gabriel synthesis of primary amines; in the previous work, Z = $\phi COCH_2$. While both the protection reactions (P,P'), with $\phi COCH_2SO_2Cl$, and deprotection, (D,D'), with zinc/acetic acid, were satisfactory, Gabriel synthesis from phenacylsulfonamide was not successful and the alkylations with R'X wastefully required two equivalents of alkylating agent since the phenacyl methylene was simultaneously monoalkylated. Furthermore, the substituted phenacylsulfonamides were found to be unstable to alkali even at room temperature.



(1)

In light of the very smooth formation and alkylation of triflamides[2,3] we were encouraged to reexamine the problem with Z = CF_3. Protection reactions (P,P') are near quantitative using the anhydride $(CF_3SO_2)_2O$ in methylene chloride with triethylamine at -78°. Reaction (P') is simpler with aliphatic secondary amines using the stable crystalline triflating agent $\phi N(SO_2CF_3)_2$ with triethylamine at room temperature,[4] the by-product N-phenyl triflamide being removed by aqueous carbonate extraction (the same reagent also effects

reaction (P) smoothly but, as both products are primary triflamides, they are not separable by extraction). The alkylations were effected with K_2CO_3/acetone at room temperature overnight. Results are summarized in Table I.

The primary triflamides are unaffected by reducing agents such as phosphines, phosphites, zinc/acid, or lithium aluminum hydride; the latter simply forms the triflamide salt. However, primary triflamides are readily reduced by Red-Al[5] in minutes in boiling benzene,[2,6] while secondary triflamides are rapidly reduced by lithium aluminum hydride in boiling ether for reactions D and D′ (Table I).

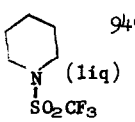
The Gabriel synthesis parallel requires alkylation of the parent triflamide anion ($CF_3SO_2NH^-$) but under a variety of conditions (controlling pH, etc.) we observed only dialkylation of the triflamide. However, this problem is easily avoided by using as the "Gabriel reagent" benzyl triflamide anion and following the alkylation with base-catalyzed elimination,[2] as shown in equation (2).

$$R\text{-}X + \overset{-}{N}SO_2CF_3 \longrightarrow \underset{CH_2\phi}{R\text{-}NSO_2CF_3} \xrightarrow{\text{base}} \left[\underset{CH\phi}{R\text{-}N}\right] \xrightarrow{H_3O} RNH_2 + \phi CHO \qquad (2)$$

Alkylation of N-benzyl triflamide with n-heptyl bromide or benzyl chloride led to the N-alkyl derivatives nearly quantitatively. The products were heated with sodium hydride in dimethylformamide at 100° (3 hours) and the crude imines hydrolyzed by refluxing in tetrahydrofuran: 10% HCl (2:1) for 3 hours. n-Heptyl and benzyl amines were formed in 80% and 84% yields, respectively (in one case 75% of benzaldehyde was isolated as a dinitrophenylhydrazone). A survey of several alkylated p-nitrobenzyl triflamides showed that K_2CO_3 was sufficient for elimination (85-95% yields) but required up to ten days in boiling acetone.[7] Attempts to make the more activated $p\text{-}CF_3SO_2C_6H_4CH_2NHSO_2CF_3$ from benzyl triflamide and triflic anhydride were unsuccessful.[7]

This alternate Gabriel reaction creates primary amines without requiring hydride reducing agents; if simple deprotection (D) of primary triflamides is required without reducing hydrides, it may also be achieved by alkylation with benzyl bromide followed by sodium hydride elimination (2).

Table I. Protection and Monoalkylation of Amines

Primary Amines	Yields [a] (P) →	← (D)	Primary Triflamides [b]	Alkylation Yields →	Secondary Triflamides [b]	Yields [a] (D') →	← (P')	Secondary Amines
ϕNH_2	97%	94%	$\phi NHSO_2CF_3$ (66-67°)	CH_3I 94%	$\phi N(CH_3)SO_2CF_3$ (liq)	90%	97%	$\phi NHCH_3$
				C_2H_5I 93%	$\phi N(C_2H_5)SO_2CF_3$ (liq)	90%	94%	ϕNHC_2H_5
				ϕCH_2Br 97%	$\phi N(CH_2\phi)SO_2CF_3$ (80-81°)	89%	--	$\phi NHCH_2\phi$
ϕCH_2NH_2	96%	95%	$\phi CH_2NHSO_2CF_3$ (39-40°)	CH_3I 95%	$\phi CH_2N(CH_3)SO_2CF_3$ (liq)	93%	--	ϕCH_2NHCH_3
				C_2H_5I 96%	$\phi CH_2N(C_2H_5)SO_2CF_3$ (liq)	88%	--	$\phi CH_2NHC_2H_5$
					 (liq)	94%	95%	

[a] (A) Yields of triflation with $(CF_3SO_2)_2O$

(B) Yields of reduction with $LiAlH_4$ for secondary amines, with Red-Al for primary amines

[b] m.p. of triflamide derivative in parentheses

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