

TRIFLAMIDES: NEW ACYLATING AND TRIFLATING REAGENTS

by James B. Hendrickson and Ray Bergeron

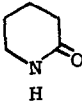
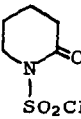
Edison Memorial Laboratory

Brandeis University, Waltham, Ma. 02154

(Received in USA 21 August 1973; received in UK for publication 5 October 1973)

The trifluoromethanesulfonyl ("triflyl") group appears to be the most powerful electron-withdrawing group known and we have been examining this effect in a series of synthetic applications.¹ Triflation of nitrogen greatly enhances the potential of that atom to act as a stabilized anion leaving group, $\text{CF}_3\text{SO}_2\text{N}^-$ (cf., $\text{CF}_3\text{SO}_2\text{NH}_2$, $\text{pK}_a = 5.8$). Accordingly, we examined the behavior of N-triflated amides as acylating agents. These acylating agents may be prepared from amides by performing the amide anion with sodium hydride (or t-butyl-lithium) in benzene and then adding triflic anhydride, $(\text{CF}_3\text{SO}_2)_2\text{O}$, at 5° C. The reaction is worked up by washing with aqueous acid and evaporation of solvent. Alternatively, acyl N-phenyl triflamides are created from acid chlorides by mixing N-phenyl triflamide with triethylamine and the acid chloride in methylene chloride at room temperature and working up in the same fashion. Examples are collected in Table I.

Table I. Formation of Triflamide Acylating Agents

Acyl source	Triflyl source	Product (m.p.)	Yield
CH_3COCl	$\phi\text{NHSO}_2\text{CF}_3$	$\text{CH}_3\text{CON}(\phi)\text{SO}_2\text{CF}_3$ (93-94°)	97%
ϕCOCl		$\phi\text{CON}(\phi)\text{SO}_2\text{CF}_3$ (97-98°)	91%
$\text{CH}_3(\text{CH}_2)_2\text{COCl}$		$\text{CH}_3(\text{CH}_2)_2\text{CON}(\phi)\text{SO}_2\text{CF}_3$ (liq.)	> 95%*
$\phi\text{CH}_2\text{COCl}$		$\phi\text{CH}_2\text{CON}(\phi)\text{SO}_2\text{CF}_3$ (liq.)	> 95%*
ϕCONHCH_2	$(\text{CF}_3\text{SO}_2)_2\text{O}$	$\phi\text{CON}(\text{CH}_2\phi)\text{SO}_2\text{CF}_3$ (93-95°)	91%
ϕCOCl	$\phi\text{CH}_2\text{NHSO}_2\text{CF}_3$	$\phi\text{CON}(\text{CH}_2\phi)\text{SO}_2\text{CF}_3$ (93-95°)	92%
	$(\text{CF}_3\text{SO}_2)_2\text{O}$	 (134°)	93%


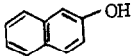
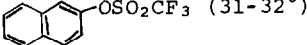

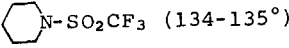
* Estimate by nmr

Two other procedures were explored. In one, the carbonyl bis-triflamide, $\text{CO}(\text{N}(\phi)\text{SO}_2\text{CF}_3)_2$ (m.p. 129-130°), was similarly prepared (90% yield) from phosgene as an analogue of carbonyl bis-imidazole. Its reaction with acids or their

anions, however, did not proceed below 70°, at which temperature bubbling ensued but no acyl triflamide could be found among the several products. Alternatively, triflic isocyanate (CF₃SO₂NCO) was prepared by triflating ethyl urethan and distilling the product from phosphorus pentoxide. This isocyanate reacts with carboxylate salts with instant bubbling of CO₂ at room temperature to form the stable salts, RCONSO₂CF₃, but these salts were recovered unchanged from normal alkylating agents.²

The acylating agents so prepared (Table I) are crystalline substances, apparently indefinitely stable to normal storage. They are less reactive than acid chloride but do react cleanly in high yield with modestly basic nucleophiles. Although stable for long periods in methanol, refluxing with an equivalent of methoxide afforded methyl esters in over 90% yield as noted in Table II. Similarly, amines were smoothly acylated in methylene chloride at room temperature in over 95% yield by these agents. Examples are collected in Table II, the products identified by comparison with authentic samples. N-acetyl-N-phenyl triflamide also proved to be far more efficacious for N-acetylation of pyrrols than acetyl-imidazole or other common acetylating agents.³ The N-phenyl triflamide formed as a by-product is readily removed by extraction with aqueous carbonate.

Table II. Acylation and Triflation by Triflamide Acylating Agents

Nucleophile	Reagent	Product (m.p.)	Yield
CH ₃ O ⁻ /CH ₃ OH	φCON(φ)SO ₂ CF ₃	φCOOCH ₃ (liq.)	94%
		CH ₃ OCO(CH ₂) ₄ NHSO ₂ CF ₃ (liq.)	93%
φNH ₂	CH ₃ CON(φ)SO ₂ CF ₃	CH ₃ CONHφ (114-115°)	92%
	φCON(CH ₂ φ)SO ₂ CF ₃	φCONHφ (163-164°)	93%
φCH ₂ NH ₂	CH ₃ CON(φ)SO ₂ CF ₃	CH ₃ CONHCH ₂ φ (60°)	97%
	φCON(φ)SO ₂ CF ₃	φCONHCH ₂ φ (105-106°)	98%
φOH	φN(SO ₂ CF ₃) ₂	φOSO ₂ CF ₃ (liq.)	95%
			91%
φNH ₂		NHSO ₂ CF ₃ (66-67°)	94%
φCH ₂ NH ₂		CH ₂ NHSO ₂ CF ₃ (39-40°)	90%
			88%
φNHCH ₃		(φN(CH ₃)SO ₂ CF ₃) (liq.)	0%
φNHC ₂ H ₅		(φN(C ₂ H ₅)SO ₂ CF ₃) (liq.)	0%

The analogous triflating agent, phenyl triflimide ($\phi\text{N}(\text{SO}_2\text{CF}_3)_2$ m.p. 93-94°) is easily prepared (92%) from reaction of aniline with two moles of the anhydride, $(\text{CF}_3\text{SO}_2)_2\text{O}$, in methylene chloride at -78° with two moles of triethylamine as base. This crystalline reagent is not hygroscopic and appears to be indefinitely stable. Its much reduced activity vis-a-vis triflic anhydride offers potentially valuable selectivity. Triflation of phenol proceeded at -78° with triethylamine in methylene chloride to phenyl triflate ($\phi\text{OSO}_2\text{CF}_3$) in 95% yield, a considerable improvement over triflation with the anhydride or with N-triflyl-imidazole.⁴

The reagent showed unexpected selectivity with amines. Reaction with aniline or benzylamine in the presence of triethylamine at room temperature yielded the corresponding triflamides of these primary amines in high yield. On the other hand the secondary aromatic amines, N-methyl- and N-ethyl-aniline, were recovered completely unchanged under the same conditions or even at elevated temperatures. Finally, the cyclic aliphatic secondary amine, piperidine, was triflated in high yield. The discrimination offered by this reagent could thus be very useful in separating primary from secondary aromatic amines, particularly taken with the easy reductive removal of the triflyl group from triflamides.^{1,5}

Triflation of carboxylate anions by the phenyl triflimide reagent represents another potential route to the acylating agents by way of equation (1). When equimolar triethylamine, acetic acid and phenyl triflimide were mixed in



methylene chloride, the initial ir spectrum shows largely the acetyl-N-phenyl triflamide peak at 1720 cm^{-1} with a small acetic anhydride absorption at 1820 cm^{-1} . Over some time, or by refluxing, the ir spectrum comes to an equilibrium which reflects the anhydride as the major component (2). The finding suggests that the acyl triflamides are somewhat more reactive than the anhydrides, and that they are not feasibly prepared by equation (1).

References

1. J. B. Hendrickson, R. Bergeron, A. Giga and D. Sternbach, J. Amer. Chem. Soc., 95, 3412 (1973).
2. Unpublished results by Dr. I. Joffe in these laboratories. It may be noted also that these acyl triflamide salts did not undergo pyrolytic α -elimination (to RNCO) but were thermally stable to 300°.
3. P. Keehn and J. Haley, private communication.
4. F. Effenberger and K. E. Mack, Tetrahedron Letters, 1970, 3947.
5. J. B. Hendrickson and R. Bergeron, submitted for publication.