A Straightforward Synthesis of Alkenyl Nonaflates from Carbonyl Compounds Using Nonafluorobutane-1-sulfonyl Fluoride in Combination with Phosphazene Bases

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This paper is dedicated to Prof. D. Seebach on the occasion of his 70th birthday.

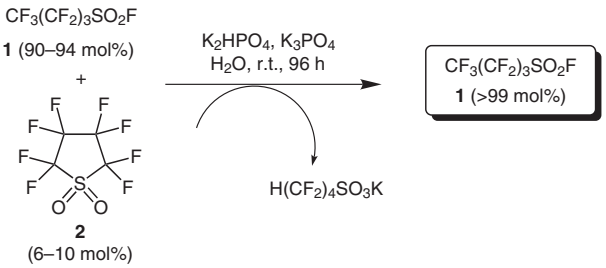
Abstract: An α-deprotonation of carbonyl compounds with phosphazene bases in the presence of the internal quenching reagent, nonafluorobutane-1-sulfonyl fluoride furnishes the corresponding alkenyl nonaflates. The new general method provides high yields of alkenyl nonaflates from aldehydes and cyclic ketones. However, it is not applicable to acyclic ketones whose nonaflate derivatives undergo fast E2 elimination to give alkynes. Successful synthesis of nonaflates from aldehydes requires carefully controlled reaction conditions to avoid the subsequent elimination to alkynes. A kinetic control enables high regioselectivities in favor of least substituted nonaflate regioisomers derived from cyclic ketones and modest *Z*-selectivities of alkenyl nonaflates derived from aldehydes. A new efficient protocol for highly selective removal of perfluorosulfolane admixture from technical nonafluorobutane-1-sulfonyl fluoride by basic hydrolysis is described.

Key words: chemoselectivity, nonafluorobutane-1-sulfonyl fluoride, ketones, regioselectivity, alkenyl nonaflates

Sulfonic acid enol esters (alkenyl sulfonates) constitute a synthetically important link that enables the extension of the transition-metal-catalyzed cross-coupling methodology to enolizable carbonyl compounds, one of the most abundant and ubiquitous pools of organic substrates. So far, alkenyl triflates proved to be the enol derivatives most frequently used in Pd(0)-catalyzed cross-coupling reactions.[1] However, alkenyl nonaflates (*nonafl*uorobutanesulfon*ates*) represent a useful alternative[2–6] to the triflates not least owing to the advantageous properties of the nonafluorobutane-1-sulfonyl fluoride (**1**, NfF),[7] a sulfonylating reagent routinely used for the preparation of the nonaflates from carbonyl derivatives.[7b,8,9] The compound **1** is a technical product obtained in 90–94% purity by the electrochemical fluorination of inexpensive 2,5-dihydrothiophene 1,1-dioxide, with perfluorosulfolane (**2**) being the admixture (6–10 mol%, see Scheme 1, left). Although the presence of the sulfolane **2** apparently does not affect the performance of alkenyl nonaflates in one-pot cross-coupling protocols,[2a,d,f,6c] it may lead to the formation of side products[7b] or deteriorate analytical characteristics of isolated nonaflates.

Herein, we would like to report on efficient purification of the technical quality nonafluorobutane-1-sulfonyl fluoride (**1**) and its application in combination with phosphazene bases for a new high-yielding synthesis of alkenyl nonaflates from enolizable carbonyl compounds.

We have found that a vigorous stirring of the technical product consisting of the perfluorinated compounds **1** and **2** with the concentrated aqueous buffer solution of K_2HPO_4 and K_3PO_4 (pH 12–13) for 96 hours at r.t. led to highly selective nucleophilic ring opening of the perfluorosulfolane (**2**) to give potassium 1,1,2,2,3,3,4,4-octafluorobutanesulfonate[10] with NfF (**1**) remaining essentially intact (Scheme 1). Phase separation followed by distillation over P_2O_5 furnished NfF (**1**; 92% yield) of >99% purity according to ^{19}F NMR.



Scheme 1 Purification of NfF by basic treatment with aqueous phosphate buffer solution

High stability of NfF (**1**) towards nucleophilic (basic) treatment (Scheme 1) prompted us to investigate a possibility of applying this pure reagent in combination with metal-free nitrogen bases[11] to obtain alkenyl nonaflates from ketones or aldehydes. After the extensive experimentation,[12] we were rewarded by finding out that (*tert*-butylimino)tris(1-pyrrolidinyl)phosphorane[13] (hereinafter called P_1-base) and 1-(*tert*-butylimino)-1,1,3,3,3-pentakis(dimethylamino)-1λ^5,3λ^5-diphosphazene (hereinafter called P_2-base[14]), commercially available representatives of the family of phosphazene bases (Figure 1), advanta-

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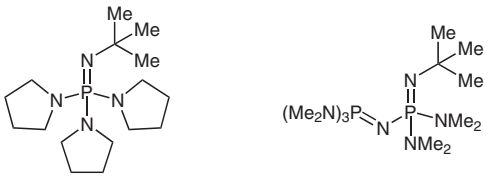
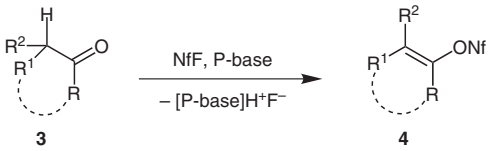


Figure 1 Phosphazene bases employed for the synthesis of alkenyl nonaflates from carbonyl compounds



Scheme 2 Synthesis of nonaflates **4** using P-bases in combination with NfF

geously introduced and developed by Schwesinger et al., are fully compatible with NfF.

This enabled us to develop a novel synthesis of alkenyl nonaflates achieved in a single operation step by having the electrophilic component NfF present during the deprotonation of the carbonyl compound[15] by the phosphazene base (Scheme 2).

The reactions were found to proceed smoothly in common nonprotogenic solvents, THF or DMF.[16]

P_1-base induced smooth and high-yielding conversion of cyclic plane-symmetric ketones **3a–e** to the desired nonaflates **4a–e**.[17] The metal-free noncoordinating nature of the P_1-base provided perfect regioselectivity control in favor of the deprotonation of the ketone **3h** at the position most remote to the ring nitrogen to give nonaflate **4h** as a single isomer.[6c,17] However, the P_1-base was found to be nonregioselective in α-methine vs. α-methylene deprotonation of 2-methyl cyclopentanone (**3f**) and 2-methyl cyclohexanone (**3g**). Fortunately, the regioselectivity was crucially improved when the much stronger P_2-base was employed under kinetically controlled conditions.[18] In both cases, the nonaflates **4f**,**g** bearing the less substituted double bonds were formed in high yields and regioselectivities.

Nonaflation of the aldehydes **3i–k** proceeded appreciably faster than that of the cyclic ketones apparently owing to higher acidity of the α-hydrogens of the aldehydes. However, in the case of **3j**,**k**, the room-temperature reactions were deteriorated by subsequent base-induced elimination of NfOH to give terminal alkynes as side products.[6c] Gratifyingly, carrying out the reactions at lower temperature (less than –30 °C) enabled a perfect kinetic discrimination between nonaflation and elimination steps in favor of the former resulting in good yields of the desired nonaflates **4j**,**k**. We believe that the observed moderate *Z*-selectivities of **4j**,**k** are owing to the stabilizing antiperiplanar overlap of the σ_{C-H} and the incipient σ^*_{C-ONf} in the open-chain transition state. It is noteworthy that the low-temperature transformation of 6-oxo-heptanal **3k** into the enol nonaflate **4k** was successfully accomplished, with unprotected ketone functionality remaining intact.

Table 1 Synthesis of Alkenyl Nonaflates **4**[a]

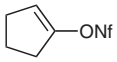
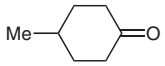
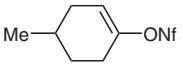
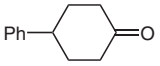
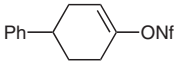
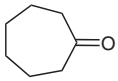
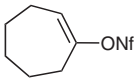
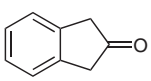
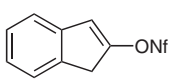
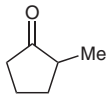
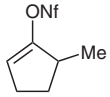
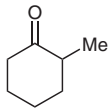
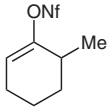
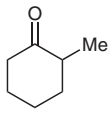
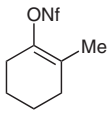
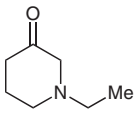
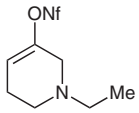
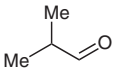
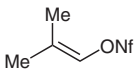
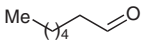
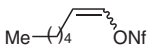
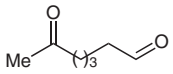
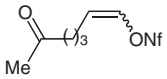
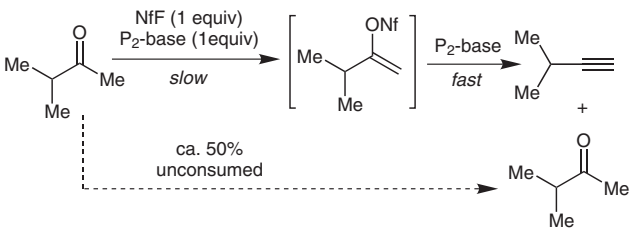
Starting material 3	Reaction conditions	Product **4**	
		Isolated yield (%) (isomer ratio)	Structure
	P_1-base, DMF, 16 h DBU, DMF, 24 h	96 94	
3a			**4a**
	P_1-base, THF, 16 h	96	
3b			**4b**
	P_1-base, THF, 20 h	95	
3c			**4c**
	P_1-base, DMF, 18 h	77	
3d			**4d**
	P_1-base, THF, 16 h DBU, THF, 24 h Et_3N,[b] DMF, 22 h	95 94 72	
3e			**4e**

Table 1 Synthesis of Alkenyl Nonaflates **4**[a] (continued)

Starting material 3	Reaction conditions	Product **4**	
		Isolated yield (%) (isomer ratio)	Structure
 **3f**	P_2-base, DMF, –30 °C, 17 h P_1-base, DMF, 21 h	84 (ca. 24:1)[c] 89 (1.3:1)[c]	 **4f**
 **3g**	P_2-base, DMF, –20 °C, 65 h[d]	93[e] (99:1)[c]	 **4g**
 **3g**	P_1-base, DMF, 111 h	84 (1:2)[c]	 **4g′**
 **3h**	P_1-base, DMF, 18 h	75	 **4h**
 **3i**	P_1-base, DMF, 4 h	89	 **4i**
 **3j**	P_1-base, DMF, –30 °C, 19 h	84 (*Z*/*E* = 4.3:1)	 **4j**
 **3k**	P_1-base, DMF, –30 °C, 21 h	93 (*Z*/*E* = 5:1)	 **4k**

[a] With P-bases (1.15 equiv) and NfF (1.15 equiv) at r.t. unless otherwise stated.[17,18]
[b] Amount of Et_3N: 4 equiv.
[c] In favor of the regioisomer shown.
[d] An 88% conversion was observed after 24 h.
[e] P-base (2.0 equiv) and NfF (2.0 equiv) were required in order to achieve a complete conversion of the starting ketone.

Acyclic ketones failed to produce alkenyl nonaflates under our reaction conditions. In a typical example, a treatment of 3-methylbutan-2-one with equimolar amounts of NfF and P_2-base at –78 °C to room temperature produced a ca. 1:1 mixture of the starting material and isopropyl acetylene (Scheme 3) suggesting that the reaction rate of the desired nonaflate formation is far lower than the following base-induced elimination of NfOH leading to the alkyne.[19]



Scheme 3

In conclusion, we have developed a general chemo- and regioselective synthesis of alkenyl nonaflates[20] from cyclic ketones and aldehydes using phosphazene bases[21] combined with nonafluorobutane-1-sulfonyl fluoride. The latter reagent was obtained in >99% purity by treatment of the industrial product of technical grade with the basic aqueous buffer. As compared to previously reported methods, our synthesis provides broader scope of application and higher yields of the requisite nonaflates from carbonyl compounds,[9] and does not require the intermediacy of trimethylsilyl enol ethers.[7b] The efficiency of the synthesis described here along with the earlier observations of higher reactivity of nonaflates as compared to the corresponding triflates in solvolysis[22] and Pd-catalyzed cross-coupling reactions[4a,5b,23] should pave the way to much broader application of the nonaflates[24] in organic synthesis.

Acknowledgment

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(3) For Negishi reaction, see: Bellina, F.; Ciucci, D.; Rossi, R.; Vergamini, P. *Tetrahedron* **1999**, *55*, 2103.

(4) For Stille reaction, see: (a) Wada, A.; Ieki, Y.; Ito, M. *Synlett* **2002**, 1061. (b) Wada, A.; Ieki, Y.; Nakamura, S.; Ito, M. *Synthesis* **2005**, 1581.

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(11) (a) Lithium amide bases readily react with NfF even at low temperature to give the anticipated nonafluorobutane-1-sulfonamides: Lyapkalo, I. M.; Reissig, H.-U.; Schäfer, A.; Wagner, A. *Helv. Chim. Acta* **2002**, *85*, 4206. (b) For this reason, only the stepwise procedure is possible. See refs. 5b and 8.

(12) Trialkylamines are not basic enough to promote the nonaflation whereas DBU gives low conversions due to the side reaction with NfF. The results will be reported in a subsequent full account.

(13) It has the highest basicity (pK_a = 28.35 in MeCN) among commercially available P_1-bases: Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435.

(14) (a) Commercially available as a 2 M solution in THF (pK_a = 33.49 in MeCN). (b) According to the primary classification given by Schwesinger, the subscript designates the number of P-atoms in the molecule. For the synthesis and properties of P_2- or higher-order phosphazene bases, see: Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G. Z.; Peters, E. M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, *7*, 1055; and references cited therein.

(15) This mode of reactivity termed as internal quenching was originally described by Corey and Gross for highly regio- and stereoselective synthesis of silyl enolates by deprotonation of carbonyl compounds with lithium dialkylamide bases in the presence of trialkylsilyl chlorides. See: Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(16) While THF is more convenient and environmentally benign solvent, DMF is found to be advantageous for the Pd-catalyzed cross-couplings of alkenyl nonaflates.[2g,5b,8] Hence, should one choose to carry out a subsequent coupling reaction without isolation of the nonaflate **4**, DMF is a preferable solvent for the one-pot nonaflation–coupling sequence.

(17) **General Procedure**: A one-necked round-bottomed reaction flask equipped with a three-way tap and a teflon-coated magnetic stirring bar was heated with a heat-gun under vacuum for a few minutes and then cooled under an atmosphere of dry argon. A solvent (1 mL), a carbonyl compound **3** (1.00 mmol) and NfF (1.15 mmol) were successively added via syringe into the reaction flask. The mixture was cooled to 0 °C under vigorous stirring before P-base (1.15 mmol) was added dropwise. The three-way tap was quickly replaced with a glass stopper, and the reaction mixture was stirred at r.t. unless stated otherwise for α-methylcycloalkanones and aldehydes **3j**,**k** (see Table 1). After the carbonyl compound **3** had been fully consumed (^{1}H NMR control), the resulting mixture was quenched with H_2O (5 mL) and extracted with pentane (4 × 25 mL). The combined organic phase was washed with H_2O (20 mL) and dried ($MgSO_4$). After the volatiles were removed carefully under reduced pressure on a rotary evaporator (≥ 100 mbar for **4a**; ≤20 °C water-bath temperature for all the compounds), the residue was subjected to flash chromatography [silica gel, pentane for **4a**–**j**, hexane–EtOAc (1:1) for **4k**] to give pure enol nonaflates **4** as colorless or yellowish liquids.

(18) Kinetically controlled nonaflation of α-methylcyclo-alkanones **3f**,**g** and aldehydes **3j**,**k** was carried out according to the above procedure except that the temperature was kept at –30 °C in the case of **3f**,**j**,**k**, and at –20 °C in the case of **3g**. For the conversion of aldehydes **3j**,**k**, 1.08 equivalents of P_1-base was used.

(19) A general synthesis of alkynes or allenes from acyclic ketones and NfF depending on the base employed and the structural features of the ketones will be described by us elsewhere: Vogel, M. A. K.; Stark, C. B. W.; Lyapkalo, I. M.; manuscript in preparation.

(20) **Spectroscopic Data**: ^{1}H NMR (400.23 MHz) and ^{13}C NMR (100.65 MHz) data in $CDCl_3$ (δ in ppm from internal $SiMe_4$) of the selected products **4** are given below. **4b**: ^{1}H NMR (400.23 MHz, $CDCl_3$): δ = 0.99 (d, ^3J = 6.4 Hz, 3 H, Me), 1.39–1.49 (1 H), 1.68–1.87 (3 H), 2.20–2.34 (2 H), 2.35–2.45 (1 H) (all m, 3 × CH_2, C*H*Me), 5.73 (m, 1 H, CH=). ^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 20.6 (Me), 27.3 (*C*HMe), 27.4, 30.6, 32.0 (all CH_2), 118.0 (*C*H=C), 149.3 (CH=*C*). **4e**: ^{1}H NMR (400.23 MHz, C_6D_6): δ = 2.99 (s, 2 H, CH_2), 6.17 (s, 1 H, CH=), 6.86–6.89 (1 H), 6.94–7.08 (all m, 3 H, CH_{Ar}). ^{13}C NMR (100.65 MHz, C_6D_6): δ = 37.5 (CH_2), 119.8 (CH=C), 122.4, 123.9, 126.3, 127.3 (all CH_{Ar}), 137.7, 140.3 (C_{Ar}), 153.7 (CH=*C*). **4h**: ^{1}H NMR (400.23 MHz, $CDCl_3$): δ = 1.13 (t, ^3J = 7.2 Hz, 3 H, Me), 2.30–2.36 (m, 2

H, CH_2), 2.56 (q, ^3J = 7.2 Hz, 2 H, NCH_2Me), 2.58 (t, ^3J = 5.8 Hz, 2 H, NC$H_2$$CH_2$), 3.14 (m, 2 H, NCH_2C=), 5.85 (m, 1 H, CH=C). ^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 12.3 (Me), 24.3 (CH_2), 48.5, 51.4, 52.6 (all NCH_2), 116.6 (*C*H=C), 146.2 (CH=*C*). (*Z*)-**4k**: ^{1}H NMR (400.23 MHz, $CDCl_3$): δ = 1.70 (m, 2 H, CH_2C$H_2$$CH_2$), 2.14 (s, 3 H, MeCO), 2.22 (q, ^3J = 7.6 Hz, 2 H, CH_2CH=), 2.46 (t, ^3J = 7.3 Hz, 2 H, $COCH_2$), 5.23 (td, ^3J = 5.6, 7.6 Hz, 1 H, C*H*=CHONf), 6.61 (br d, ^3J = 5.6 Hz, 1 H, CH=C*H*ONf). ^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 22.4, 23.6, 42.6 (all CH_2), 29.9 (Me), 119.4 (*C*H=CHONf), 136.2 (CH=*C*HONf), 208.0 (C=O). (*E*)-**4k**: ^{1}H NMR (400.23 MHz, $CDCl_3$, non-overlapping signals only): δ = 2.08 (q, ^3J = 7.7 Hz, 2 H, CH_2CH=), 5.74 (dt, ^3J = 7.7, 11.8 Hz, 1 H, C*H*=CHONf), 6.56 (br d, ^3J = 11.8 Hz, 1 H, CH=C*H*ONf). ^{13}C NMR (100.65 MHz, $CDCl_3$): δ = 22.6, 26.0, 42.3 (all CH_2), 30.0 (Me), 121.7 (*C*H=CHONf), 136.8 (CH=*C*HONf), 207.9 (C=O).

(21) Although we did not aim at recovering phosphazene bases from side products, phosphazenium fluorides, the bases could be recovered via crystallization of their salts followed by treatment with a sufficiently strong inorganic base.[13,14] We are currently working on the procedure employing catalytic quantities of the phosphazene bases in combination with heterogeneous strong inorganic base NaH or KH.
(22) Subramanian, L. R.; Hanack, M. *Chem. Ber.* **1972**, *105*, 1465.
(23) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203.
(24) Nonaflate anion can easily be precipitated from aqueous solutions in form of a stable, non-hygroscopic potassium salt which is described as an efficient flame retardant additive in transparent polycarbonate compositions. See: (a) Singh, R. K.; Lin, Y.-G. U.S. Patent Appl., US 2005009968, **2005**. (b) Singh, R. K.; Rosenquist, N. R.; Fischer, J. M. U.S. Patent Appl., US 6462111, **2002**.