

NEW PALLADIUM-CATALYZED ADDITION OF CYANOTRIMETHYLSILANE TO
F-ALKYLATED 1-AZA-1,3-DIENES. A CONVENIENT ROUTE TO β,γ -UNSATURATED
 α -F-ALKYL- α -AMINO ACID PRECURSORS

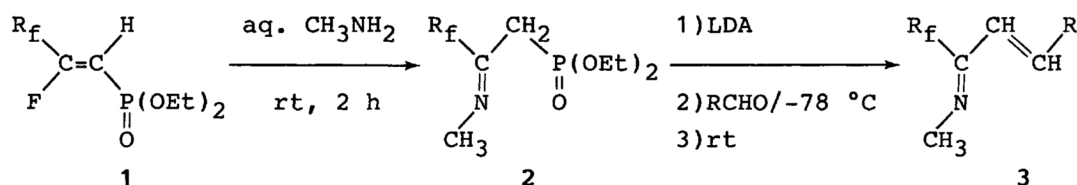
Yasuhiro YAMASAKI, Takashige MAEKAWA, Takashi ISHIHARA,* and Teiichi ANDO
 Department of Industrial Chemistry, Faculty of Engineering,
 Kyoto University, Yoshida, Kyoto 606

2-F-Alkylated 1-aza-1,3-dienes, easily prepared from
 1H-F-1-alkenephosphonates, smoothly underwent the addition
 of cyanotrimethylsilane in the presence of a catalytic amount
 of palladium(II) acetate or chloride to give β,γ -unsaturated
 α -F-alkyl- α -amino nitriles and/or γ -F-alkyl- γ -amino nitriles
 in good yields.

There is increasing interest in partially fluorinated organic compounds
 owing to their specific properties,¹⁾ especially biological or physiological
 activities. Amino acids, including β,γ -unsaturated ones,^{2a-c)} are one of the
 most important, bioactive compounds²⁾ and, therefore, the development of the
 method for the synthesis of such compounds bearing an F-alkyl substituent is of
 much value both synthetically and biologically.³⁾

In our continuing studies to extend the synthetic utilities of fluoro
 alkenephosphonates and their derivatives,⁴⁾ we have found that 2-F-alkylated 1-
 aza-1,3-dienes can be prepared in two steps from 1H-F-1-alkenephosphonates and
 that they react readily with cyanotrimethylsilane under the influence of a
 transition metal salt.

This communication describes a new addition of cyanotrimethylsilane to 2-
F-alkyl-1-aza-1,3-dienes catalyzed by a palladium(II) salt or trimethylsilyl
 triflate, which can serve as a convenient route to β,γ -unsaturated α -F-alkyl- α -
 amino acids.



1-H-F-1-Alkenephosphonates (1) were allowed to react with aqueous methyl-
 amine in ether at room temperature to give β -iminoalkanephosphonates (2) in
 high yields.⁵⁾ Treatment of the phosphonates (2) with lithium diisopropylamide
 (LDA) in ether at -78°C followed by addition of an aldehyde afforded trans
 isomers of the corresponding 2-F-alkyl-1-aza-1,3-dienes (3) in good yields,⁶⁾

which could be isolated by column chromatography on silica gel. The yields of **3** and their vinylic coupling constants are summarized in Table 1.

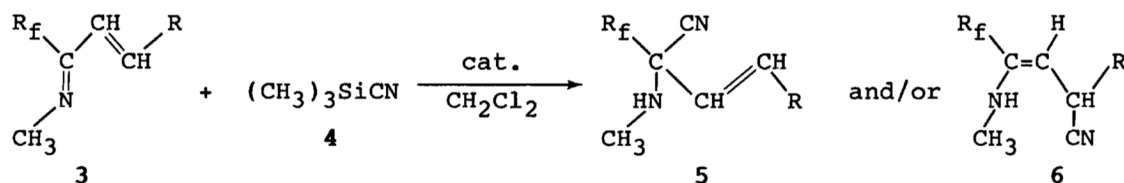
Table 1. Synthesis of 1,3-dienes (**3**)

R_f	R	Yield of 3 /%	$J_{HH}/\text{Hz}^a)$
CF_3	$n\text{-C}_6\text{H}_{13}$	77	17.0
CF_3	$c\text{-C}_6\text{H}_{11}$	75	15.0
CF_3	Ph	77	18.0
CF_3CF_2	$n\text{-C}_6\text{H}_{13}$	88	16.5
CF_3CF_2	$c\text{-C}_6\text{H}_{11}$	95	17.4
CF_3CF_2	Ph	95	18.0
CF_3CF_2	<u>trans</u> - $\text{CH}_3\text{CH}=\text{CH}$	79	<u>b)</u>

a) The values are the coupling constants between two vinylic protons on newly-formed double bond.

b) The coupling constant could not be determined.

Cyanotrimethylsilane (**4**), a useful reagent for introducing a cyano group, is known to add readily to carbonyl and imino compounds in the presence of a Lewis acid such as zinc iodide, aluminium(III) chloride, and titanium(IV) chloride.⁷⁾ These Lewis acids, however, were not effective at all for the addition of **4** to the imino functional group of 2-F-alkylated 1-aza-1,3-dienes (**3**), resulting in the formation of complex products.



Transition metal salts are expected to allow this reaction to proceed successfully, by virtue of their coordination to an olefinic linkage. In fact, palladium(II) salts were found to promote the addition reaction of **4** efficiently. When F-alkylated 1-aza-1,3-dienes **3** were treated with cyanotrimethylsilane **4** in the presence of a catalytic amount (20 mol%) of palladium(II) acetate or chloride, the corresponding β,γ -unsaturated α -F-alkyl- α -amino nitriles (**5**)⁶⁾ and/or γ -F-alkyl- γ -amino nitriles (**6**)⁶⁾ were obtained in good yields through 1,2- and 1,4-addition of **4**, respectively. The results of the reaction are summarized in Table 2. This reaction did not occur in the absence of palladium(II) salt. Salts of other transition metals such as tetrakis-(triphenylphosphine)palladium(0) and dichlorobis(triphenylphosphine)nickel(II) did not effect the present addition reaction, the starting 1-aza-1,3-dienes being recovered unchanged. The contents of 1,2-adducts (**5**) in the product are

in the range of 65-100%. Of most significance is that in the case of F-alkylated 1-aza-1,3-dienes (3) bearing an additional conjugative group such as propenyl or phenyl, the addition reaction of 4 proceeded regioselectively to give 1,2-adduct (5) exclusively.

Table 2. Reaction of 2-F-alkyl-1,3-dienes (3) with 4

R _F	R	Conditions ^{a)}	Ratio of 5/6	Total yield/%	J _{HH} /Hz ^{b)}
CF ₃	<u>n</u> -C ₆ H ₁₃	A	43/57	82	-
		B	76/24	80	15.0
CF ₃	<u>c</u> -C ₆ H ₁₁	A	40/60	83	-
		B	74/26	64	15.9
CF ₃	Ph	C	100/0	86	16.5
		B	100/0	54	16.5
CF ₃ CF ₂	<u>n</u> -C ₆ H ₁₃	A	11/89	89	-
		B	73/27	63	15.0
		D	74/26	57	-
		E	-	0 ^{c)}	-
CF ₃ CF ₂	<u>c</u> -C ₆ H ₁₁	A	18/82	91	-
		B	65/35	76	15.9
CF ₃ CF ₂	Ph	A	100/0	89	16.5
		B	100/0	43	16.5
CF ₃ CF ₂	<u>trans</u> -CH ₃ CH=CH	F	100/0	36	15.3
		G	100/0	40	15.3

a) A: (CH₃)₃SiOTf 10 mol%, 4 d; B: Pd(OAc)₂ 20 mol%, 4 d; C: (CH₃)₃SiOTf 10 mol%, 2 d; D: PdCl₂ 20 mol%, 4 d; E: without Pd(II) salt; F: (CH₃)₃SiOTf 10 mol%, 1 d; G: Pd(OAc)₂ 20 mol%, 3 d.

b) The values present the coupling constants between vinylic protons in the 1,2-adducts 5.

c) The starting material 3 was recovered.

Table 2 also shows the results of the reactions conducted by use of trimethylsilyl triflate. With a catalytic amount of trimethylsilyl triflate instead of palladium(II) salt, the compounds (6) were mainly obtained in good yields. Even in the presence of this catalyst, however, only the corresponding 1,2-adducts (5) were formed from 2-F-alkyl-1-aza-1,3-dienes (3) carrying a conjugative group.

The general procedure for the present reaction is as follows: β-Imino-alkanephosphonate (2) (5 mmol) was added to an ethereal solution of LDA (6 mmol) at -78 °C and the mixture was allowed to warm up to 0 °C over 30 min. An aldehyde (5.5 mmol) was added dropwise to the resulting mixture at -78 °C. After being stirred overnight at room temperature, the reaction mixture was quenched with aqueous NH₄Cl and was subjected to extraction with ether. The

usual treatment gave the product (3). A mixture of α -alkyl-1-aza-1,3-dienes (3) (1 mmol), cyanotrimethylsilane (4) (3 mmol), and palladium(II) acetate (0.2 mmol) in CH_2Cl_2 (2.5 ml) was stirred at room temperature for 4 days under a nitrogen atmosphere. The reaction mixture was poured onto a mixture of ether (10 ml) and aqueous 5% NaOH (10 ml) followed by filtration through a Celite bed, extraction with ether, drying (Na_2SO_4), and evaporation. Chromatography on silica gel of the crude product gave pure β,γ -unsaturated α - α -alkyl- α -amino nitriles (5) and/or γ - α -alkyl- γ -amino nitriles (6).

References

- 1) For example, F. A. Smith, *Chemtech*, **1973**, 422; R. Filler, *ibid.*, **1974**, 752; T. S. Lin, C. Chai, and W. H. Prusoff, *J. Med. Chem.*, **19**, 915 (1976); C. Walsh, *Tetrahedron*, **38**, 871 (1982); R. Filler and Y. Kobayashi, "Biomedical Aspects of Fluorine Chemistry," Kodansha Ltd and Elsevier Biomedical, Tokyo and New York (1982).
- 2) For example, a) P. Bey and J. P. Vever, *J. Org. Chem.*, **45**, 3249 (1980); b) Y. Kuroda, M. Okuhara, T. Goto, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, **33**, 132 (1980); c) A. J. L. Cooper, S. M. Fitzpatrick, C. Kaufman, and P. Dowd, *J. Am. Chem. Soc.*, **104**, 332 (1982); d) C. N. C. Drey, "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," B. Weinstein, Ed., Marcel Dekker, New York (1977).
- 3) For recent reports on the synthesis of fluorinated α -amino acids and related compounds, see: P. Bey, J. P. Vever, V. V. Dorsselaer, and M. Kolb, *J. Org. Chem.*, **44**, 2732 (1979); P. Bey, J. B. Ducep, and D. Schirlin, *Tetrahedron Lett.*, **25**, 5657 (1984); T. Tsushima, K. Kawada, J. Nishikawa, T. Sato, K. Tori, T. Tsuji, and S. Misaki, *J. Org. Chem.*, **49**, 1163 (1984); T. Tsushima and K. Kawada, *Tetrahedron Lett.*, **26**, 2445 (1985); I. Ojima, K. Hirai, M. Fujita, and T. Fuchikami, *J. Organomet. Chem.*, **279**, 203 (1985), and references cited therein.
- 4) T. Ishihara, T. Maekawa, and T. Ando, *Tetrahedron Lett.*, **24**, 4229 (1983); T. Ishihara, T. Maekawa, and T. Ando, *ibid.*, **25**, 1377 (1984); T. Ishihara, Y. Yamasaki, and T. Ando, *ibid.*, **26**, 79 (1985).
- 5) Other primary amines including hydroxylamine and ammonia were found to react with 1 to afford the corresponding phosphonates 2 in 60-90% yields. The phosphonates 2 carrying $\text{R}_f=\text{CF}_3$ exist as a mixture of imino and enamino isomers (1 : 1), which are effective for the subsequent reaction.
- 6) The spectral (IR, MS, ^1H , and/or ^{19}F NMR) and analytical data pertaining to all compounds were consistent with the assigned structures.
- 7) D. A. Evans, *J. Chem. Soc., Chem. Commun.*, **1973**, 55; I. Ojima, S. Inaba, K. Nakatsugawa, and Y. Nagai, *Chem. Lett.*, **1975**, 331; I. Ojima, S. Inaba, and Y. Nagai, *ibid.*, **1975**, 737; P. G. Gassman and J. J. Talley, *Tetrahedron Lett.*, **1978**, 3773; K. Utimoto, M. Obayashi, and Y. Shishiyama, *ibid.*, **21**, 3389 (1980); W. J. Greenlee, *J. Org. Chem.*, **49**, 2632 (1984); M. E. LeTourneau and J. R. McCarthy, *Tetrahedron Lett.*, **25**, 5227 (1984).

(Received July 5, 1985)