

# SYNLETT Spotlight 267

## Trimethylsilylacetonitrile (TMSAN)

Compiled by Penélope Merino-Montiel



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

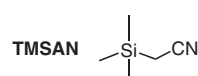
Penélope Merino-Montiel was born in 1982 in Puebla, Mexico. She obtained her B.Sc. degree in Chemistry from Benemérita Universidad Autónoma de Puebla. She was involved in undergraduate research in steroidal chemistry under the guidance of Professor Jesús Sandoval and Socorro Meza. Currently she is carrying out her Ph.D. in the Organic Chemistry Department of the Universidad de Sevilla, Spain under the supervision of Professor José Fuentes. Her research focuses on the synthesis of spironucleosides derivatives.

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 1203, E-41071 Seville, Spain  
E-mail: pmlp@us.es

### Introduction

Trimethylsilylacetonitrile (TMSAN) is a popular commercial reagent that has been used in the synthesis of several useful synthetic building blocks. TMSAN is usually used as a nucleophile, mainly in additions to a carbonyl group,<sup>1</sup> in order to obtain cyanomethylated adducts, or in

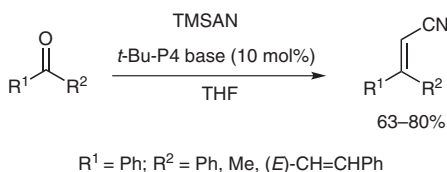
nucleophilic substitution reactions, for example in the preparation of functionalized cyclopropanes.<sup>2</sup>



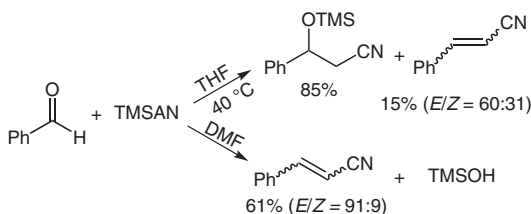
Scheme 1

### Abstracts

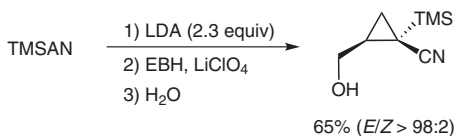
(A) The condensation of TMSAN with ketones in the presence of the catalytic *t*-Bu-P4 base to give cyanoalkenes has been reported;<sup>3</sup> title compounds were prepared in a 63–80% yield. The reaction was also extended to the condensation of TMSAN with *N*-arylformanilides (ArNRCHO) in the preparation of enamine derivatives.



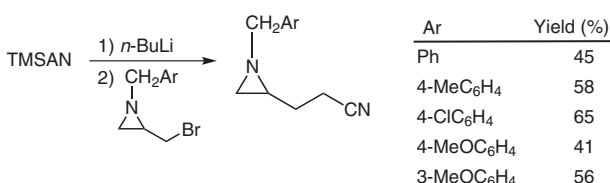
(B) The addition of TMSAN to the carbonyl group of benzaldehyde catalyzed by KF/Al<sub>2</sub>O<sub>3</sub> in THF allows the preparation of 3-phenyl-3-(trimethylsilyloxy)propionitrile as the major product (85%), together with cinnamitrile (15%). A change of the solvent to DMF leads to the  $\alpha,\beta$ -unsaturated nitrile as main product (61%).<sup>4</sup>



(C) Langer and co-workers reported a one-pot cyclization of epibromohydrin (EBH) with TMSAN in the presence of a strong base and catalyzed by a Lewis acid to form trimethylsilylcyclopropane with excellent diastereoselectivity (*E*/*Z* > 98:2) and moderate yield (65%).<sup>5</sup>



(D) Recently, 2-(2-cyanoethyl)aziridines were obtained by treatment of TMSAN with an equimolecular amount of *n*-BuLi followed by the addition of 1-arylmethyl-2-(bromomethyl)-aziridines.<sup>6</sup> Title compounds were obtained in moderate yield (41–65%).



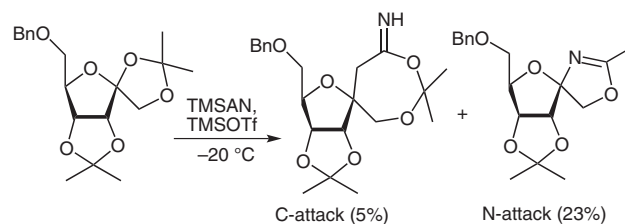
SYNLETT 2009, No. 3, pp 0507–0508

Advanced online publication: 06.02.2009

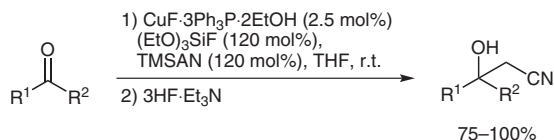
DOI: 10.1055/s-0028-1083572; Art ID: V27108ST

© Georg Thieme Verlag Stuttgart · New York

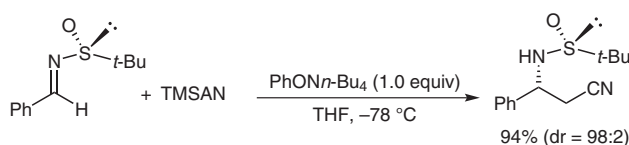
(E) TMSAN has been used as a nucleophile to open the acetal ring in sugar spiroketals. The nucleophilic attack of TMSAN on the anomeric carbon can take place either through the nitrogen atom or through the methylenic carbon<sup>7</sup> to give a spironucleoside or a spiro-C-glycoside, respectively.



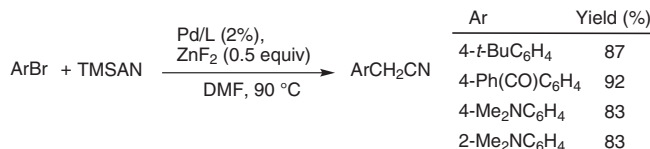
(F) There are a few reports of cyanomethylation of aldehydes and ketones using TMSAN as nucleophile. Suto et al. have developed a copper fluoride catalyzed addition to the carbonyl group with high yields.<sup>8</sup>



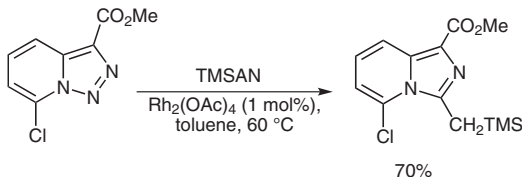
(G)  $\beta$ -Amino nitriles can be obtained by the condensation between chiral *N*-(*tert*-butylsulfonyl)imines and TMSAN in the presence of a Lewis base with excellent diastereoselectivity.<sup>9</sup> Optimization of the reaction conditions by changing the Lewis base, temperature, and solvent showed that the best yields and diastereoisomeric ratios were obtained when  $\text{PhON}n\text{-Bu}_4$  was used as a Lewis base in THF at  $-78^\circ\text{C}$ .



(H) Wu and Hartwig described the monoarylation of nitriles by means of the coupling of TMSAN with aryl halides in the presence of palladium catalysts and zinc fluoride.<sup>10</sup>



(I) A singular reaction of transannulation of pyridotriazoles with TMSAN in the presence of  $\text{Rh}_2(\text{OAc})_4$  to afford a *N*-fused imidazopyridine was described by Chuprakov et al.<sup>11</sup> Rhodium-catalyzed transannulations of 1-sulfonyl triazoles were recently reported by the same group.<sup>12</sup>



(J) Nakao et al. reported the Ni-catalyzed carbocyanation of 4-octyne with TMSAN in the presence of a Lewis acid (LA) to give a highly substituted allylsilane in modest yield (29%).<sup>13</sup>



## References

- (1) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2005**, 34, 1508.
- (2) Langer, P.; Freifeld, I. *Org. Lett.* **2001**, 3, 3903.
- (3) Kobayashi, K.; Ueno, M.; Kondo, Y. *Chem. Commun.* **2006**, 3128.
- (4) Kawanami, Y.; Yuasa, H.; Toriyama, F.; Yoshida, S.; Baba, T. *Catal. Commun.* **2003**, 4, 455.
- (5) Albrecht, U.; Freifeld, I.; Reinke, H.; Langer, P. *Tetrahedron* **2006**, 62, 5775.
- (6) D'hooghe, M.; Vervisch, K.; De Kimpe, N. *J. Org. Chem.* **2007**, 72, 7329.
- (7) Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, 12, 1267.
- (8) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, 5, 3147.
- (9) Mukaiyama, T.; Michida, M. *Chem. Lett.* **2007**, 36, 1244.
- (10) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, 127, 15824.
- (11) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2007**, 46, 4757.
- (12) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. *J. Am. Chem. Soc.* **2008**, 130, 14972.
- (13) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, 129, 2428.