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Fluoride Ion Mediated Peterson Alkenation of N-[C,C-bis(Trimethylsilyl)methyl]amido Derivatives with Carbonyl Compounds: A Short General Route to Enamides and 1,2-Dihydroisoquinolines.

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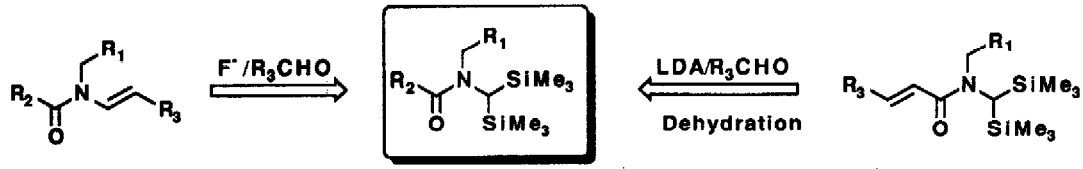
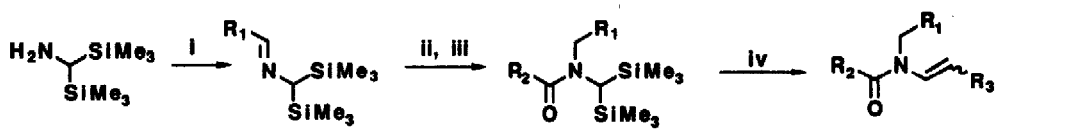
Abstract: A straightforward general access to diversely substituted acyclic or cyclic enamides and dienamides is accomplished by using a fluoride induced Peterson olefination of carbonyl compounds and enolizable amides derived from C,C-bis(trimethylsilyl) methylamine.

Formation of a carbon-carbon bond from α-metallo amines is fraught with difficulties associated with the generation of the corresponding α-amino carbanions[1]. Although several procedures have been developed recently to solve this problem[2], the introduction of new and simple methodologies to form α-nitrogen carbon-carbon bonds is of considerable interest. Particularly, the regioselective generation of carbanions adjacent to the nitrogen atom in the presence of other enolizable functionalities remains a challenging synthetic task. One of the more promising approaches to this problem is the fluoride ion mediated cleavage of silicon-carbon bonds[3] in mono- and bis- C-trimethylsilylmethylamides, followed by carbonyl trapping or Peterson olefination. This methodology has been developed simultaneously by Snieckus[4] and by our group[5]. The ortho directed metallation *versus* fluoride-induced dual behaviour described by Snieckus suffers, however, from a severe synthetic limitation because the strong base/trimethylchlorosilane mediated preparation of the required N-[C,C-bis(trimethylsilyl)methyl]amides is limited to benzamido derivatives or other α-proton free amides. Now, we wish to report the advantages of the use of C,C-bis(trimethylsilyl)methylamine **1**[6] as a key intermediate for the preparation of N-[C,C-bis(trimethylsilyl)methyl]amides, including those carrying enolizable protons, and their dual bias as base-promoted enolates or fluoride-promoted α-amido carbanions. This fully regiocontrolled carbanion generation allows a short general synthesis of both open chain and cyclic enamides, and more particularly, of the synthetically very useful dienamides[7].



As illustrated in Scheme 1, our approach to enamides **8-10** involved prior formation of N-protected-N-[C,C-bis(trimethylsilyl)methyl] amido derivatives **4-7** from C,C-bis(trimethylsilyl) methylamine[8] **1**. The N-alkylation in compounds **4-7** was necessary in order to avoid the presence of adjacent acidic protons during the α-amino carbanion generation and the benzyl group was chosen preferently because of its easy removal under non hydrolytic conditions. Treatment of the amine **1** with different benzaldehydes and subsequent reduction of the resulting Schiff bases **2** and **3** with sodium borohydride afforded the corresponding N-benzylamines, which were subjected to further acylation under standard conditions to give the expected N-benzyl-N-[C,C-bis(trimethylsilyl) methyl] amides **4-7** in 68 - 87 % overall yield.



1

2 R_1: C_6H_5
3 R_1: 2-$MeO_2CC_6H_4$

4 $R_1 = C_6H_5$ $R_2 = CH_3$
5 $R_1 = C_6H_5$ $R_2 = MeOCH_2$
6 $R_1 = R_2 = C_6H_5$
7 R_1 = 2-$MeO_2CC_6H_4$ $R_2 = C_6H_5$

8 $R_1 = C_6H_5$ $R_2 = CH_3$
9 $R_1 = C_6H_5$ $R_2 = MeOCH_2$
10 $R_1 = R_2 = C_6H_5$

a R_3: C_6H_5 **b** R_3: 4-MeC_6H_4 **c** R_3: 4-$MeOC_6H_4$ **d** R_3: ^tBu **e** R_3: $C_6H_5CH{=}C(Me)$

Scheme 1 . Reagents and conditions: **i** R_1CHO, C_6H_6, 80°C (Dean-Stark), 2h **ii** $NaBH_4$ (4 equiv.), MeOH, 0°C→r.t., 2h **iii** R_2COCl, NEt_3, CH_2Cl_2, 0°C→r.t., 2h. **iv** R_3CHO,THF, Bu_4NF, r.t., 2h.

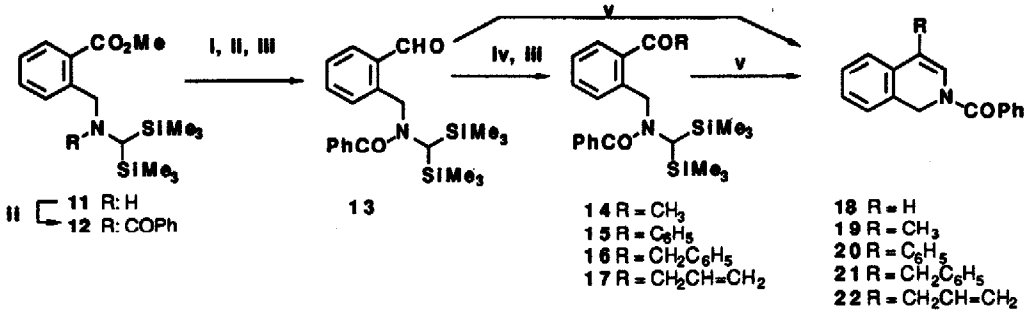
We first examined the olefination of **4** with 4-methylbenzaldehyde to determine the best reaction conditions for this Peterson type reaction. After several runs to establish the optimum compromise between reaction solvent, fluoride ion source and catalyst amount, we found that the addition of a stoichiometric amount of anhydrous tetrabutylammonium fluoride (TBAF) in THF gave the best results, yielding the expected enamide **8b** in 60% isolated yield, accompanied by a slight amount of the corresponding monodesilylated derivative of **4** as the sole byproduct. When other solvents like methylene chloride or N,N-dimethylformamide were used to carry out the reaction, a loss of chemical reactivity was observed with recovery of the starting aldehyde and formation of the monodesilylated product of amide **4** . The use of a catalytic amount (~10% molar) of TBAF or TASF in either THF or methylene chloride[5] resulted in a partial conversion (typically 10-40% after 20h) and the desired enamide was accompanied by comparable amounts of protodesilylation product. Once we had established the optimum reaction conditions, we continued our work following the operation mode described above and we extended the olefination reaction to different carbonyl compounds and N-[C,C-bis(trimethylsilyl)methyl] amides. Some representative examples are given in the Table.

Entry	Compound	Yield,%[a] (E:Z)[b]	Entry	Compound	Yield,%[a] (E:Z)[b]	Entry	Compound	Yield,%[a] (E:Z)[b]
1	**8b**	60(35:65)	6	**10d**	65(30:70)	11	**21**	55(--)
2	**8c**	70(38:62)	7	**10e**	71(50:50)	12	**22**	48(--)
3	**9a**	72(46:54)	8	**18**	50(--)	13	**29**	53(50:50)
4	**9d**	77(50:50)	9	**19**	58(--)	14	**30**	55(45:50)
5	**10a**	76(50:50)	10	**20**	67(--)	15	**31**	62(50:50)

[a] Non optimized yields of pure isolated products by column chromatography and Kugelrohr distillation. [b] E:Z molar ratio determined by ^{1}H-NMR (300 MHz) spectroscopy by integration of enamide signal at δ= 5.5-6.7 ppm.

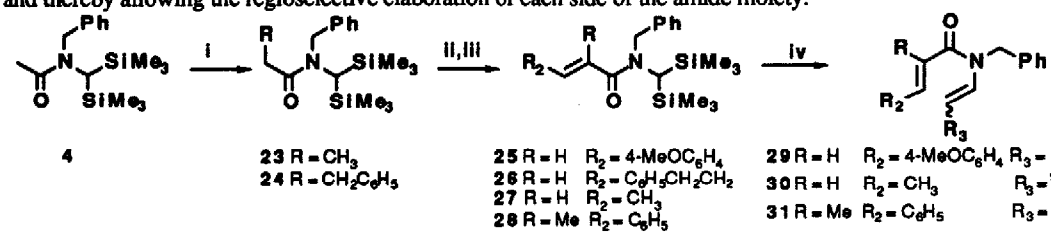
As shown in the Table, the enamides **8-10** were obtained in fairly good yields both from non enolizable amides (entries 5,6) and from enolizable ones (entries 1-4), giving mixtures of E and Z isomers in which the Z isomer usually predominated. Enolizable carbonyl compounds, however, failed to give the expected reaction, although the use of α,β-unsaturated carbonyl compounds as substrates (entry 7) allowed a straightforward preparation of N-dienyl amides, an important class of Diels-Alder dienes[9]. The next aspect we investigated was the intramolecular version of the above methodology (Scheme 2). To test the intended cyclization, we first tried to prepare the required key carbonyl compound **13** by DIBAL reduction of the ester **12**. Unfortunately, a mixture of the corresponding benzyl alcohol and the starting ester (1: 2 molar ratio) was produced instead of the expected benzaldehyde **13**. The problem was finally solved by performing the reduction of the methoxycarbonyl group in **11** and protecting the resulting hydroxy derivative with N-trimethylsilyloxazolidinone (TMSO)[10] and further N-benzoylation and oxidation by means of the triphosgene-dimethylsulfoxide system[11] to provide the

aldehyde **13** in 42 % overall yield. Grignard addition to the formyl group was followed by triphosgene-dimethylsulfoxyde oxidation of the resultant carbinols to furnish ketones **14 - 17** in 46 - 68 % overall yields. When **13** was treated with TBAF (1 equiv.) in THF as solvent (entry 8), a dark colour appeared inmediately and smooth reaction took place giving the 1,2-dihydroisoquinoline **18** in 50% isolated yield. Similarly, compound **14-17** furnished their corresponding 1,2-dihydroisoquinolines **19-22** in 48-66% yield. It is noteworthy that in these intramolecular reactions the presence of enolizable α-protons in the carbonyl moiety (entries 9 and 11) does not seem to constitute a limitation, as indicated by the fact that no appreciable protodesilylation byproducts were detected in the crude reaction mixtures by ^{1}H-NMR analysis.



Scheme 2. Reagents and conditions: **i** $LiAlH_4$ (2 equiv.), Et_2O, 0°C→r.t., 15h. then$TMSO,CH_2Cl_2$, $ClSiMe_3$ cat., 20°C, 2h **ii** PhCOCl, NEt_3, CH_2Cl_2, 0°C→ r.t., 2h. **iii** $Cl_3COCO_2CCl_3$, DMSO, NEt_3, CH_2Cl_2, -78°C→ r.t., 2h. **iv** RMgBr, THF, 0°C, 40min-5h **v** Bu_4NF, THF, r.t., 2h.

Finally, the dual carbanion generation potential of N-[C,C-bis(trimethylsilyl)methyl] amides was examined. As illustrated in Scheme 3, the use of bases like LDA provoked selective abstraction of the enolizable protons in acetamides like **4** without affecting the α-nitrogen position which is strongly stabilized by the two silicon atoms, and thereby allowing the regioselective elaboration of each side of the amide moiety.



Scheme 3. Reagents and conditions: **i** LDA, THF, R-I (2 equiv.), -10°C→r.t., 20h. **ii** LDA, THF, R_2CHO, -78°C→r.t., 15h. **iii** $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0°C→ r.t., 2h. **iv** Bu_4NF, THF, R_3CHO, r.t., 2h.

Thus, the alkylation with methyl iodide or benzyl bromide of the lithium enolate of acetamide **4** under standard conditions gave the respective propionamides **23** and **24** in 73% and 87% isolated yield. Similarly, aldols were obtained in yields ranging from 65 to 93% when the lithium enolates of amides **4**, **23** or **24** were reacted with carbonyl compounds. Dehydration of the resulting β-hydroxyamides through a mesylation-elimination sequence provided the corresponding α,β-unsaturated N-[C,C-bis(trimethylsilyl)methyl] amides **25-28** in nearly quantitative yields as E isomers. Once the carbonyl moiety has been elaborated, the above described fluoride ion promoted olefination could be applied to the nitrogen moiety affording the expected dienamides **29-31** in 53 - 62 % yield.

The present method demonstrates a new synthetic application of C,C-bis(trimethylsilyl) methylamine in organic synthesis and sets the basis for its extension to other heterocyclic compounds of biological interest.

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REFERENCES AND NOTES:

1. For reviews, see: a) Beak, P.; Reitz, D.B., *Chem. Rev.*, **1978**, *78*, 275. b) Seebach, D. *Angew. Chem. Int. Ed. Engl.* , **1979**, 239. c) Beak, P.; Zajdel, W.J.; Reitz, D.B., *Chem. Rev.*, **1984**, *84*, 471. d) Saavedra, J.E. in "Umpoled Synthons', Hase, T.A. Ed. Wiley. New York, **1987**, p. 101. Gawley, R.E.; Rein, K. in "Comprehensive Organic Synthesis", Trost, B.M.: Fleming, I. Eds. Pergamon. Oxford, **1991**, vol. 3, p. 65.

2 a) Pearson, W.H.; Lindbeck, A.C., *J. Org. Chem.*, **1989**, *54*, 5651. b) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.-Ichi; Ito, S., *Tetrahedron Lett.*, **1991**, *32*, 1975. c) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.*, **1992**, *57*, 794 and references cited therein.

3 a) Furin, G.G.; Vyazankina, O.A.; Gostevsky, B.A.; Vyazankin, N.S., *Tetrahedron*, **1988**, *44*, 2675. For seminal work on α-silyl aminoderivatives, see: a) Katritzky, A.R.; Sengupta, S., *Tetrahedron Lett*, **1987**, *28*, 5419. b) Shimizu, S.; Ogata, M., *J. Org. Chem.*, **1988**, *53*, 5160.

4 a) Cuevas, J. -C.; Snieckus, V., *Tetrahedron Lett.*, **1989**, *30*, 5837. b) Cuevas, J. -C.; Patil, P.; Snieckus, V., *Tetrahedron Lett.*, **1989**, *30*, 5841. For reviews, see: a) Snieckus, V., *Pure Appl. Chem.*, **1990**, *62*, 671, b) Snieckus, V., *Chem. Rev.*, **1990**, *90*, 879.

5 a) Palomo, C.; Aizpurua, J. M.; García, J. M.; Ganboa, I.; Cossío, F. P.; Lecea, B.; López, C., *J. Org. Chem.*, **1990**, *55*, 2498. b) Lasarte, J.; Palomo, C.; Picard, J. P.; Dunogues, J.; Aizpurua, J. M., *J. Chem. Soc.; Chem. Commun.* **1989**, 72. c) Palomo, C.; Aizpurua, J. M.; García, J. M.; Picard, J. P.; Dunogues, J., *Tetrahedron Lett.*, **1990**, *31*, 1921.

6. a) Picard, J. P.; Grelier, S.; Dunogues, J.; Aizpurua, J.M.; Palomo, C., *J. Organometal. Chem.*, **1991**, 419, C1. b) Palomo, C.; Aizpurua, J.M.; García, J.M.; Legido, M., *J. Chem. Soc; Chem. Commun.* **1991**, 524.

7. For a review concerning the preparation and synthetic applications of enamides, see: Campbell, A.L.; Lenz, G.R., *Synthesis*, **1987**, 421.

8. C,C-bis(trimethylsilyl) methylamine **1**: Chlorobis(trimethyl silyl)methane (27.2 g, 140 mmol) was added to a suspension of sodium azide (10.9 g, 168 mmol) and tetrabutylammonium bromide (0.2 g, cat.) in dry hexamethylphosphoric triamide (70 mL) and the mixture was stirred at room temperature for 2 h. On completion, the mixture was poured into water (200 mL), the aqueous solution was extracted with hexane (3 x 50 mL), and the combined organic phases were dried and evaporated at reduced pressure maintaining the temperature below 25ºC to afford crude azidobis(trimethylsilyl)methane, which was inmediately dissolved in anhydrous diethyl ether (50 mL) and added dropwise during 30 min over a suspension of lithium aluminium hidride (7.0 g, 175.5 mmol) in dry diethyl ether (220 mL). After the ebullition of the solvent caused by the exothermic reaction ceased, the mixture was stirred at room temperature for 1h. Then it was cooled with an ice-water bath and water (15 mL) was dropped carefully over the stirred reaction mixture until a white suspension of aluminium salts was obtained. The ethereal phase was separated by filtration, dried and evaporated to afford crude C,C-bis(trimethylsilyl) methylamine which was purified by reduced pressure distillation (14.3 g, 76% overall from chlorobis(trimethylsilyl)methane). B.p. 68ºC/20mmHg. ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 1 H, CH), 1.10 (s, 2 H, NH_2), 0.02 (s, 18 H, $SiCH_3$).

9. For reviews, see: a) Smith, M. B. *Org. Prep. Proc. Int.*, **1990**, *22*, 315. b) Boger, D.L.; Weinreb, S.N., "Hetero Diels-Alder Methodology in Organic Synthesis", Academic Press, Ed. Wasserman, H.H. 1987.

10. Aizpurua, J.M.; Palomo, C.; Palomo, A. L. *Canad. J. Chem.*, **1984**, *62*, 336.

11. Palomo, C.; Cossio, F.P.; Ontoria, J.M.; Odriozola, J.M. *J. Org. Chem.*, **1991**, *56*, 5948.

12. Physical and spectroscopic data of selected enamides: **18**: Oil. ^{1}H NMR ($CDCl_3$) δ 7.72-7.03 (m, 9 H, arom.), 6.54 (d, 1 H, J= 7.3 Hz, CH=), 5.75 (d, 1 H, J=7.3 Hz, CH=), 5.02 (s, 2 H, CH_2). **19**: Oil. ^{1}H NMR ($CDCl_3$) δ 7.54-7.22 (m, 9 H, arom.), 6.42 (s, 1 H, CH=), 5.01 (s, 2 H, N-CH_2), 1.96 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ 168.7, 134.0, 133.1, 130.7, 128.7, 128.1, 127.7, 127.4, 125.8, 124.9, 121.9, 115.9, 45.5, 15.9 **20**: Oil. ^{1}H NMR ($CDCl_3$) δ 7.70-7.09 (m, 14 H, arom.), 6.64 (s, 1 H, CH=), 5.10 (s, 2 H, N-CH_2). ^{13}C NMR ($CDCl_3$) δ 169.2, 171.6, 142.5, 136.9, 131.1, 126.2, 124.7, 124.1, 115.5, 45.5. **29**(E): Oil. ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1 H, J= 15.6Hz, CH), 7.35 (d, 2 H, arom), 7.33-7.2 (m, 10 H, arom), 6.83 (d, 2 H, arom), 6.80 (d, 1 H, J= 15.6Hz, CH), 4.77 (s, 2 H, N-CH_2), 3.80 (s, 3 H, MeO).

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