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α′,α′-DISILYLATED TERTIARY BENZAMIDES AS DUAL ORTHO- AND α′-CARBANION SYNTHONS. AMIDE PETERSON OLEFINATION ROUTES TO N-BENZOYL ENAMINES, ISOQUINOLINES, AND DIBENZAZOCINES

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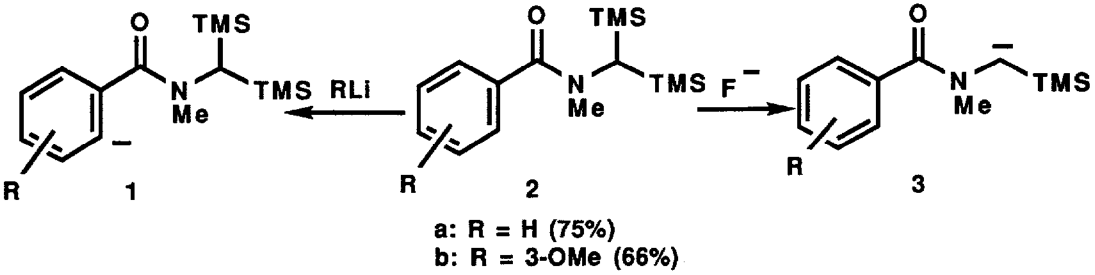
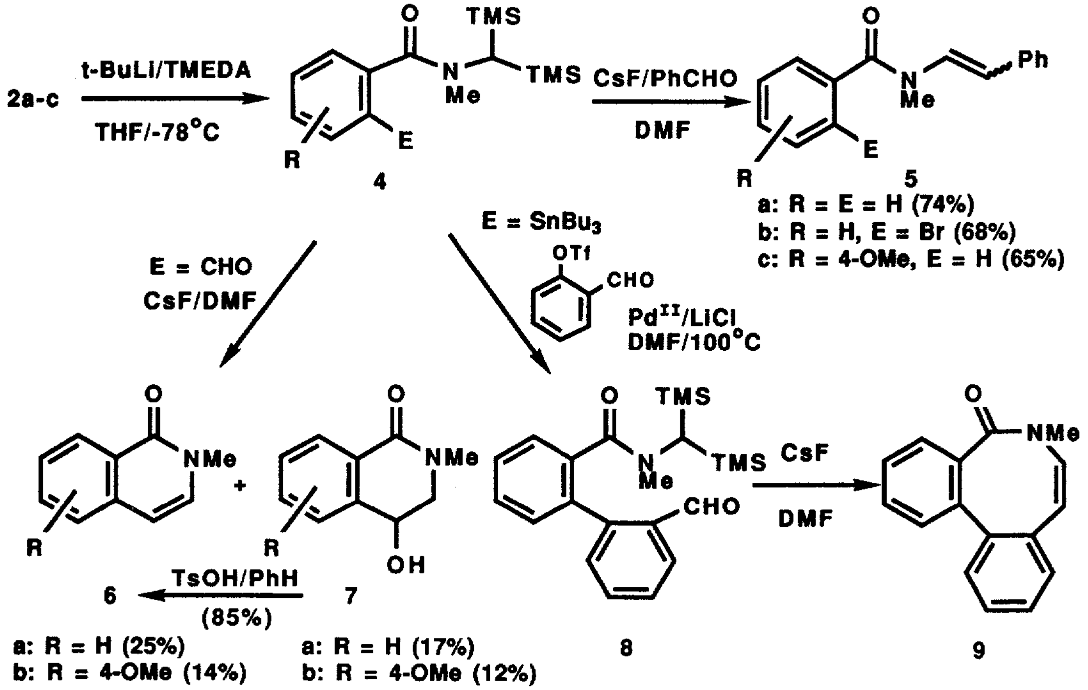
Summary: α′,α′-Disilylated benzamides **2**, prepared by LiTMP/TMSCl *in situ* trap procedure, constitute ortho- and α′-carbanion synthons which provide N-benzoyl enamines (**5**), isoquinolines (**6**), dibenzoazocines (**9**) by Peterson olefination, and pyrroles (**11**) by cycloaddition. The conversion of **2** into other useful functionality is described.

We report that Martin's compatible base/electrophile combination (LiTMP/TMSCl) for thermodynamic *in situ* ortho silylation of aromatic esters, nitriles, and sulfones[1] applied to N,N-dimethylbenzamides leads instead to α′,α′-disilylation (**2**).[2] The thereby derived N-[(bistrimethylsilyl)methyl]benzamides exhibit dual directed ortho metalation (**1**) and α′-carbanion (**3**) reactivity, useful for new intra- and inter-molecular amide Peterson olefination[3] routes to N-benzoyl enamines, quinoline, and dibenzoazocine derivatives. Furthermore, **2** and the corresponding thioamide **10**, as their imidate salts provide links to the synthetically valuable 1,3-dipolar cycloaddition protocol.[4] Aside from inherently broadening the scope of the powerful aromatic directed metalation strategy,[5,6] system **2** constitutes by the expedient of fluoride ion desilylation, a dimethylamide equivalent and thereby overcomes the perplexing problem of hydrolytic stability of the widely used N,N-diethylamide ortho metalation director.[7]



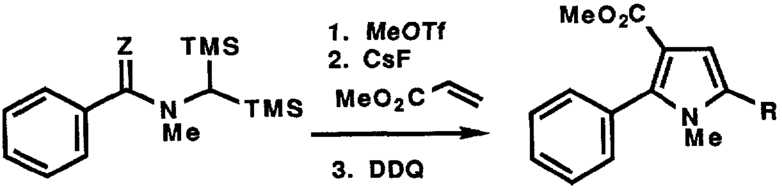
a: R = H (75%)
b: R = 3-OMe (66%)
c: R = 4-OMe (47%)

Addition of N,N-dimethylbenzamide (1 equiv) to LiTMP/TMSCl (2:10 equiv) at -78°C in THF solution afforded **2a**[8] in good yield.[9] Similarly, the disilylated methoxybenzamides **2b**, **2c** were obtained in somewhat lower yields. Results summarized in the **Table** demonstrate the smooth directed metalation chemistry of **2a-c** leading to ortho-substituted products **4a-j**. In a typical procedure, metalation (t-BuLi/TMEDA, 1:1) of **2a** in THF at -78°C followed by quench with MeOD afforded **4a** in quantitative yield. Of synthetic significance is the regiospecific formation of **4i** in good yield. In order to eliminate the mechanism of initial deprotonation at the methine site followed by intramolecular proton transfer, the 2,6-dideuterio derivative of **2a**, prepared from **4a** under the same conditions, was subjected to reaction with t-BuLi/TMEDA followed by MeOH quench. No d-incorporation at the methine position was detected (NMR, MS) indicating the operation of a proximity effect-driven [8a] aromatic deprotonation mechanism.



Treatment of α',α'-disilylated benzamides **2a**, **4f**, and **2c** with benzaldehyde under CsF/DMF conditions[6] afforded the N-benzoyl enamines **5a-c** (Z:E = 2:3) respectively in good yields. The intramolecular counterpart of this amide Peterson olefination was carried out on the o-formyl derivatives **4d** and **4j** to afford mixtures of cyclized products **6a,b** and **7a,b** in modest yields. The overall conversion into isoquinolones **6** was improved by acid-catalyzed dehydration of **7**. Taking advantage of the significant Stille methodology,[10] the stannylated **4g** was cross coupled with salicylaldehyde triflate to give biphenyl **8** (40%) which, upon CsF treatment afforded the dibenzazocine **9** (40%). The barrier for amide *syn-anti* interconversion in **4** and **8**, obligatory for cyclization, is apparently overcome under the conditions of the reaction.

The viability of the α′,α′-disilylated benzamides as 1,3-dipole synthons was exemplified by subjecting **2a** and **10**[11] to sequential reaction with methyl triflate, CsF/methyl acrylate,[4] and DDQ oxidation to give a mixture of pyrroles **11a** (25%,41%) and **11b** (13%, 0%) respectively.



2a (Z = O), 10 (Z = S)

11
a: R = H
b: R = TMS

Table. Ortho-Substituted Disilylated Benzamides 4

Compound	R	E (E$^+$)	Yield, %	mp °C
4a	H	D (MeOD)	98	oil
4b	H	Me (MeI)	91	61-62
4c	H	$CH_2CH=CH_2$ ($BrCH_2CH=CH_2$)	84	oil
4d	H	CHO (DMF)	87	74-75
4e	H	$CONEt_2$ ($ClCONEt_2$)	71	111-112
4f	H	Br (Br_2)	80	77-78
4g	H	$SnBu_3$ ($ClSnBu_3$)	98	oil
4h	H	S-t-Bu [(t-BuS)$_2$]	68	62-63
4i	3-OMe	TMS (TMSCl)	81	85-86
4j	4-OMe	CHO (DMF)	80	65-66

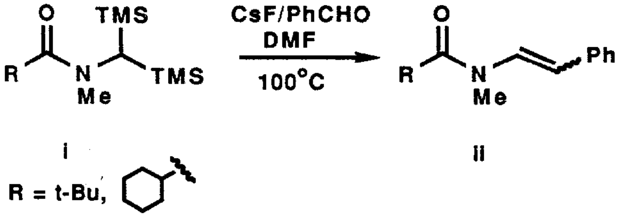
To illustrate the advantage of α′,α′-disilylated **2** (and, by implication, the corresponding α′-silylated amide[6]) over the N,N-diethylamide[5] in functional group manipulations subsequent to directed ortho metalation chemistry, compounds **2a**, **4e**, and **4h** were sequentially desilylated (TBAF/THF/RT) and reduced to give the corresponding benzaldehyde [Et_3BHLi (1,1 equiv) /THF/-20 → 0°C] or benzyl alcohol [Et_3BHLi (4,5 equiv) /THF/reflux)[12] derivatives in 71-98% yields.

In summary, we have described new α',α'-disilylated[13] and α'-silylated[6] carboxamide directed ortho metalation groups. The former, unmasked by fluoride for ready manipulation to other functionality, is a potential replacement for the diethylamide in ortho lithiation chemistry.[5] In addition, the ortho- and α'-carbanion reactivities of these systems, used inter- or intra-molecularly, provides new methods of functionalization and heterocyclization which should contribute to the further evolution of the aromatic directed metalation strategy.[14,15]

References and Footnotes

[#] NATO Postdoctoral Fellow, 1987-89.

1. Krizan, T.D.; Martin, J.C. J. Am. Chem. Soc. **1983**, 105, 6155. For other *in situ* lithiation/trap systems, see Beak, P.; Lee, B. J. Org. Chem. **1989**, 54, 458 and Eaton, P.E.; Martin, R.M. ibid. **1988**, 53, 2728 and references cited therein.
2. This result is foreshadowed by the pioneering study of Beak, P.; Brubaker, G.R.; Farney, R.F. J. Am. Chem. Soc. **1976**, 98, 3621.
3. Peterson reaction involving amides are rare; for another variation, see Sibi, M.P.; Dankwardt, J.W.; Snieckus, V. J. Org. Chem. **1986**, 51, 271. For reactions involving trimethylsilylmethyl-amines and -imines, see Lasarte, J.; Palomo, C.; Picard, J.P.; Dunogues, J.; Aizpurua, J.M. J. Chem. Soc. Chem. Commun. **1989**, 72 and references therein.
4. Vedejs, E.; West, F.G. Chem. Rev. **1986**, 86, 941.
5. Snieckus, V. Bull. Soc. Chim. Fr. **1988** (II), 67; Beak, P.; Snieckus, V. Acc. Chem. Res. **1982**, 15, 306.
6. See also Cuevas, J.-C.; Snieckus, V. Tetrahedron Lett. preceding communication.
7. The tertiary amide and the oxazoline constitute the most widely applied carbon-based directed metalation groups. Reliable protocols for conversion of oxazolines to other useful functionality have been developed, c.f. Reuman, M.; Meyers, A.I. Tetrahedron **1985**, 41, 837. A reductive sequence for N,N-diethylbenzamides to benzaldehydes is available: Sibi, M.P.; Shankaran, K.; Hahn, W.R.; Alo, B.I.; Snieckus, V. Tetrahedron Lett. **1987**, 28, 2933.
8. Based on mechanistic work a) Beak, P.; Meyers, A.I. Acc. Chem. Res. **1986**, 19, 356, conformational studies on benzamides b) Jones, P.R.; Weisman, G.R.; Baillargeon, M.J.; Gosink, T.A. J. Org. Chem. **1980**, 45, 3618, and evidence that amides of the type RCONR(CH$_2$SiMe$_3$) show strong Si-CO coordination c) Hillyard, R.W.; Ryan, C.N.; Yoder, C.H. J. Organomet. Chem. **1978**, 153, 369, the *syn* rotamers for **2** and, by implication, for **4** are provisionally assigned.
9. The LDA/TMSCl combination (c.f. Corey, F.J.; Gross, A.W. Tetrahedron Lett. **1984**, 25, 495) provided **2a** in 66% yield. Under the LiTMP/TMSCl conditions, diethyl and piperidino benzamides give only o-silylation products (see also reference 2).
10. Stille, J.K. Angew. Chem. Int. Ed. Engl. **1986**, 25, 508.
11. Prepared either by LiTMP/TMSCl treatment of N,N-dimethyl thiobenzamide (67%) or by reaction of **2a** with Lawesson's reagent/PhH/reflux (60%).
12. Brown, H.C.; Kim, S.C.; Krishnamurthy, S. J. Org. Chem. **1980**, 45, 1. Attempts to use this and other hydride reducing agents on corresponding diethylamides led either to no reaction or reduction to the benzylamines.
13. We have recently found that α',α'-disilylated aliphatic amides **i** are also obtained under the LiTMP/TMSCl conditions and lead, by reaction with CsF/PhCHO, to N-acyl enamines **ii**. The scope of the α',α'-disilylation reaction on amides and related functionality (e.g. **10**) bearing potential synthetic complement to the thoroughly investigated dipole-stabilized carbanion methodology (Beak, P.; Zajdel, W.J.; Reitz, D.B. Chem. Rev. **1984**, 84, 471) is under study.



14. All yields are unoptimized. All new compounds show analytical and spectral (IR, NMR, MS) data consistent with the assigned structures.
15. The support of our synthetic programs by NSERC, Merck Frosst Canada, and NATO (J.-C.C.) is gratefully acknowledged.

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