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α'-SILYLATED TERTIARY BENZAMIDES AS DUAL ORTHO- AND α'-CARBANION SYNTHONS. CARBODESILYLATIVE ROUTES TO ISOQUINOLINE AND DIBENZOQUINOLIZIDINE DERIVATIVES

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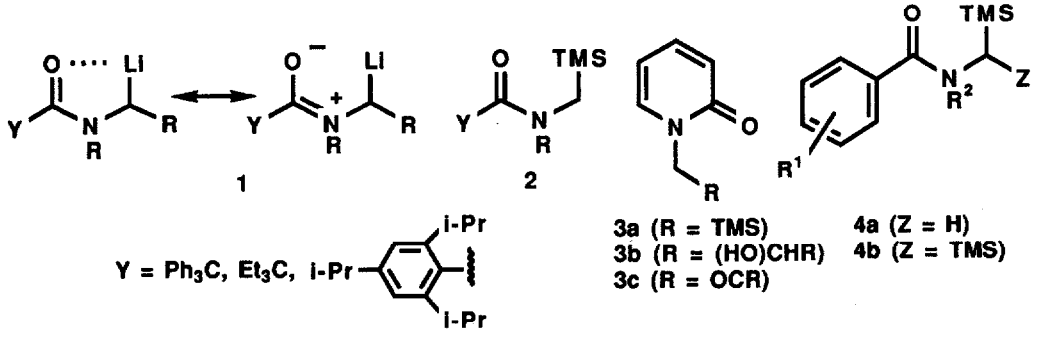
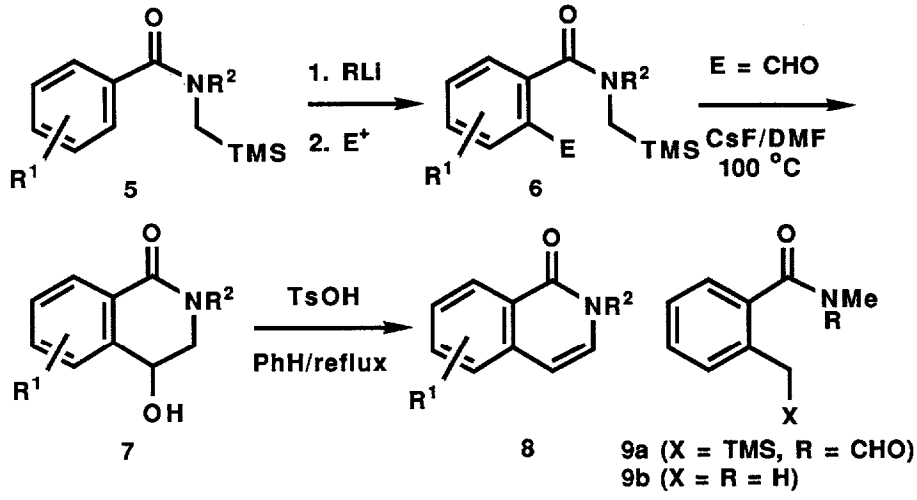
Summary: α'-Silylated benzamides **4a** display both ortho (**6**)- and α'-carbanion (**5h, 15**) reactivities which are translated into new synthetic routes for isoquinoline (**8, 18, 19**) and protoberberine (**11, 12**) derivatives.

Dipole-stabilized carbanions have emerged as promising synthetic intermediates for umpolung amine functionalization.[1] For α'-amide carbanions (**1**), utility is at times compromised by low kinetic acidity of the α-hydrogens, dimerization of **1** with its precursor, and severe conditions for hydrolysis of the necessarily highly hindered amide to achieve a general amine synthesis. Katritzky and Sengupta have recently introduced a silylated equivalent (**2**) of **1** by demonstrating the fluoride-mediated hydroxyalkylation and acylation of the silylated 2-pyridone **3a** with aldehydes and acid chlorides to give derivatives **3b**, **3c**.[2] In the course of efforts to circumvent the refractory nature of the N,N-diethylamide to hydrolysis and thereby enhance its synthetic utility in directed ortho metalation chemistry,[3] we prepared the new silylated benzamides **4a**, **4b**. In this Letter, we demonstrate the dual ortho metalation and α'-carbanion reactivities of **4a**. These properties form the basis of new routes to isoquinolones, 4-aryl tetrahydroisoquinolines and dibenzoquinolizidines by intra- and inter-molecular carbodesilylative hydroxyalkylation processes. In the accompanying Letter,[4] we describe parallel studies with **4b** leading to other heterocycles and define functional group interconversions of this masked dimethylamide. Together, these results broaden and diversify the scope of the original concept[2] and suggest new methods for heteroannelation formulated on regiospecific directed ortho metalation tactics.



Metalation (*sec*-BuLi/TMEDA/THF/-78°C/1 h) of **5**, R^1 = H, R^2 = Me[5] followed by DMF quench led only to the self-condensation product **6**, R^1 = H, R^2 = Me, E = COPh (70%) thus paralleling results obtained in the LiTMP deprotonation of N,N'-dimethylbenzamide.[6] The advantageous effect of increasing the bulk at the amide carbonyl was seen from metalation of **5a** under the same conditions which furnished, after DMF treatment, the ortho-formyl product **6a** in good yield (**Table**).[7] Similarly, the preparation of the methoxy (**6b-c**) and phenyl (**6d**) substituted derivatives was achieved from **5b-c** and **5d** respectively. Substituted benzamides **5e-g** were converted into aldehydes **6e-g** using t-BuLi/TMEDA/THF/-100 °C/1 h; DMF conditions. Treatment of these products with anhydrous CsF in DMF at 90°C afforded the hydroxy dihydroquinolones **7a-g** which were spectroscopically characterized and directly subjected to p-toluensulfonic acid-catalyzed dehydration to give the isoquinolones **8a-g**. To illustrate potential for extension to more condensed heterocycles, compound **10**, prepared by benzylic silylation (LiTMP/TMSCl),[4] was similarly treated to give **11** and **12** which represent the protoberberine alkaloid skeleton.[8] In a variation of this carbodesilylative cyclization, imide **9a**[9] was subjected to the CsF/DMF conditions to yield **8**, R^1 = H, R^2 = Me and **9b** (1:2, 63%), an indication that, presumably because of the less reactive formyl group, the desired process is in unfavorable competition with desilylation and deformylation.



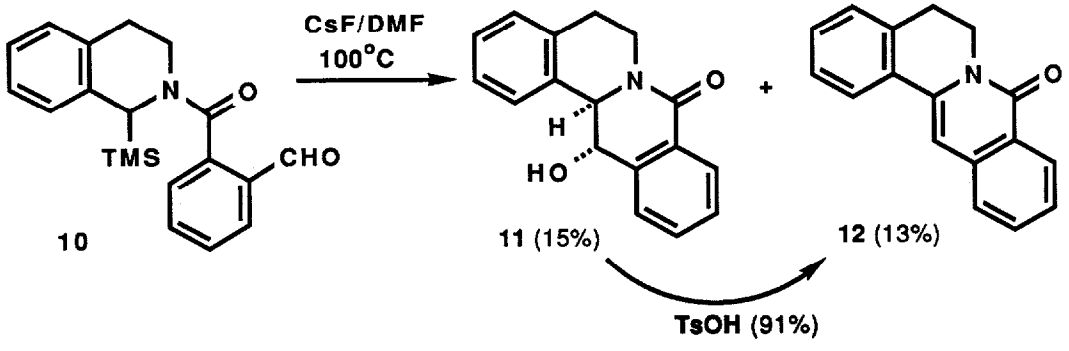
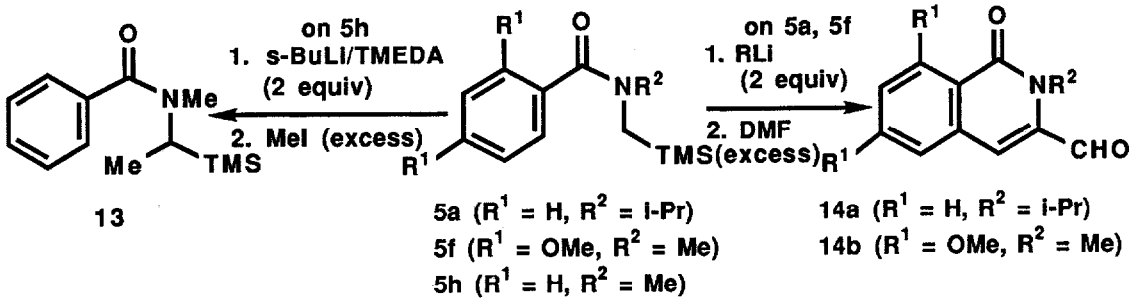


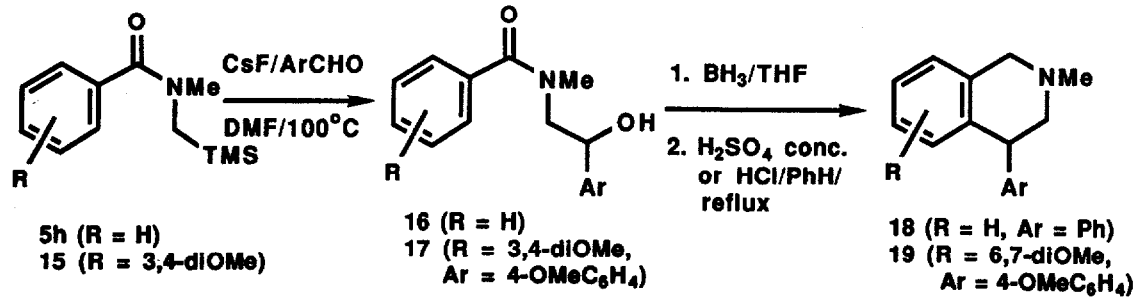
Table. Directed Metalation-Carbodesilylation Route to Isoquinolones.

Substrate 5			Product 6 (E = CHO)				Product 8			
	R^1	R^2		R^1	R^2	Yield, %		R^1	R^2	Yield, % (mp, °C)
5a	H	i-Pr	**6a**	H	i-Pr	62	**8a**	H	i-Pr	71 (104-105)
5b	3-OMe	i-Pr	**6b**	3-OMe	i-Pr	33	**8b**	5-OMe	i-Pr	68 (oil)
5c	4-OMe	i-Pr	**6c**	4-OMe	i-Pr	64	**8c**	6-OMe	i-Pr	77 (109-110)
5d	2-Ph	i-Pr	**6d**	6-Ph	i-Pr	55	**8d**	8-Ph	i-Pr	92 (115-116)
5e	2-OMe	Me	**6e**	6-OMe	Me	65	**8e**	8-OMe	Me	70 (105-106)
5f	2,4-diOMe	Me	**6f**	4,6-diOMe	Me	30	**8f**	6,8-diOMe	Me	78 (100-101)
5g	2-Cl	Me	**6g**	6-Cl	Me	24	**8g**	8-Cl	Me	84 (93-94)

Treatment of **5h** with 2 equiv of *sec*-BuLi/TMEDA followed by excess MeI quench gave **13** (18%) in addition to **6**, R^1 = H, R^2 = Me, E = COPh (32%). Applications of these conditions on **5a** but using DMF as the electrophile furnished the 3-formyl isoquinolone **14a** (40%) together with **6a** (10%). Similarly, **5f** gave the 6,8-dimethoxy analogue **14b** (49%). This preliminary evidence for formation of ortho, α'-dilithiated species may also have synthetic value.



To show utility of the intermolecular carbodesilylation reaction, **5h** and **15** were converted into the amide carbinols **16**[10] (76%) and **17** (25%) which upon diborane reduction and acid-catalyzed cyclization furnished **18** and the dimethyl ether of the 4-arylisoquinoline alkaloid, cherylline (**19**)[8a] (15% overall yield).



This work establishes the dual ortho- and α'-carbanion reactivities of **4a** and illustrates, by intra- and inter-molecular carbodesilylation pathways, its value for isoquinoline ring construction. Advantages over known methods[11] for the preparation of specifically substituted isoquinolines are derived from the regiospecific nature of the directed ortho metalation process. These and the complimentary results on **4b**,[4] which include mild conditions for manipulation of desilylated dimethylbenzamides into other useful functionality, are promising indications of α'-silylated benzamide potential in modern aromatic chemistry.[12,13]

References and Footnotes

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5. Compounds **5a-h** were prepared by treatment of the appropriate secondary amide with chloromethyltrimethyl silane under NaH/DMF/RT conditions.

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7. Other electrophiles can also be incorporated, e.g. **6**, R^1 = H, E = D(MeOD) (92%) and Me (MeI) (94%).

8. a) Shamma, M.; Moniot, J.L. Isoquinoline Alkaloids Research 1972-1977; Plenum Press: New York, **1978**. b) For an alternative route involving fluoride-induced intramolecular benzylic silane-imminium salt carbodesilylation, see Takano, S.; Numata, H.; Ogasawara, K. Heterocycles **1983**, 20, 117.

9. Prepared from the corresponding acid chloride (Chenard, B.L.; Slapak, C.; Anderson, D.K.; Swenton, J.S. J.C.S., Chem. Commun. **1981**, 179) by treatment with methyl formamide (NaH/THF/RT).

10. This reaction was first achieved by Katritzky and Sengupta (ref 2, footnote 16 and Sengupta, S. personal communication).

11. Grethe, G. Chem. Heterocyclic Compds. **1981**, 38, 1.

12. All new compounds show analytical and spectral (IR, ^{1}H NMR, MS) data in consonance with their assigned structures. Reported yields are of isolated (chromatographed) materials.

13. We are indebted to Professor A.R. Katritzky and Dr. S. Sengupta for a preprint of ref 2, correspondence and stimulation of our efforts. We are grateful to R.J. Mills for initial studies and to NSERC, Merck Frosst Canada, and NATO (J.-C.C.) for financial support.

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