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α-Aryl *O*-Vinyl Carbamates. Tandem Carbolithiation – α-Alkylation and -[1,2]-Wittig Rearrangement Reactions

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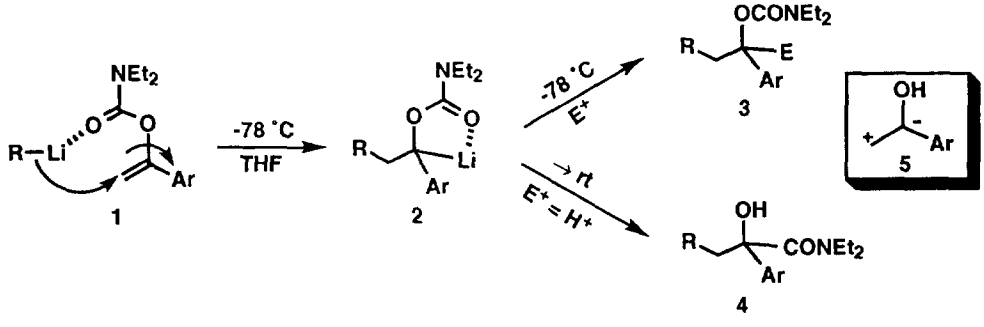
Abstract: Efficient, one-pot carbolithiation - α-alkylation and -[1.2]-Wittig rearrangement processes of α-aryl *O*-vinyl carbamates **1** to branched benzyl *O*-carbamates **3** and 2-aryl-2-hydroxypropionamides **4**, including Naproxen analogues, is described.

We report on new one-pot tandem carbolithiation – α-alkylation and -[1,2]-Wittig rearrangement regimens of α-aryl *O*-vinyl carbamates **1**[1] (**Scheme 1**) which lead efficiently to branched benzyl *O*-carbamates and 2-aryl-2-hydroxypropionamides (mandelic amides) **4**, thereby constituting a 1,2-dipole synthetic equivalent **5**.[2] Although, with a venerable exception,[3] carbolithiation of isolated and unstrained double bonds is of limited preparative value,[4] recent results show its promise in regioselective addition of alkyllithiums to allylic alcohols[5] and amines[6] in the presence of TMEDA and a (-)-sparteine-induced asymmetric version has been achieved.[7] The heretofore unobserved facility of this type of reaction,[8] presumably promoted by a Complex Induced Proximity Effect (CIPE)[9] of the carbamate donor and stability of a benzylic anion (**2**), may have general significance in the design of new carbolithiations and find synthetic application in the ibuprofen/naproxen antiinflammatory agent field.[10]

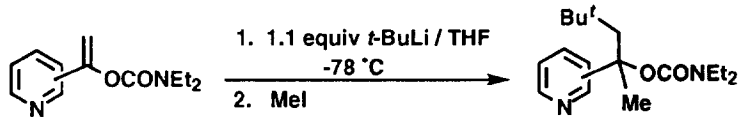
Scheme 1



Results of the one-pot reaction (**Table 1**) allow provisional evaluation of its scope and limitations. Unlike MeLi,[11] the standard RLi reagents all underwent smooth addition; quench of the intermediate species with alkyl, allyl, and benzyl bromides afforded good to excellent yields of products **3**. Quenching with TMSCl furnished an α–silyl carbamate (entry 4) and use of PhSeCl gave, as expected, ketones (entry 12). Inadvertedly explored[2] cases (entries 11, 13) illustrate additional scope for the carbolithiation.

Interestingly, *t*-BuLi (but not *n*-BuLi) also added cleanly to pyridyl *O*-vinyl carbamates **6a,b** (**Scheme 2**) with minimal pyridyl ring addition to furnish, after MeI quench, products **7a,b** in useful yields.

Scheme 2



6a, 6b(a: 2-Py; b: 3-Py) **7a (61%), 7b (62%)**

Table 1. Tadem β-Carbolithiation - α-Alkylation on α-Aryl *O*-Vinyl Carbamates 1

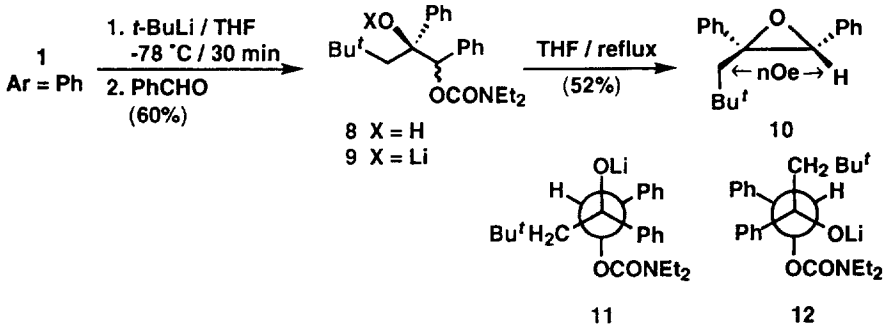
Entry	RLi	E^+	Product 3			yld, [a] %
			R	E	Ar	
1	*n*-BuLi	MeI	*n*-Bu	Me	Ph	80
2	*n*-BuLi		*n*-Bu		Ph	64
3	*n*-BuLi	$PhCH_2Br$	*n*-Bu	CH_2Ph	Ph	66
4	*n*-BuLi	TMSCl	*n*-Bu	TMS	Ph	82
5	*s*-BuLi	MeI	*s*-Bu	Me	Ph	80
6	*t*-BuLi	MeOD	*t*-Bu	D	Ph	96[b]
7	*t*-BuLi	MeI	*t*-Bu	Me	Ph	90
8	*t*-BuLi	EtI	*t*-Bu	Et	Ph	71
9	*t*-BuLi		*t*-Bu		Ph	61
10	*t*-BuLi	$PhCH_2Br$	*t*-Bu	CH_2Ph	Ph	80
11	*t*-BuLi	MeI	*t*-Bu	Me	$(3\text{-MeO})C_6H_4$	78
12	*t*-BuLi	PhSeCl	$(3\text{-MeO})C_6H_4COCH_2Bu^t$			45
13	*t*-BuLi	MeI	*t*-Bu	Me	$(3\text{-Et}_2NOC)C_6H_4$	50

[a] Ylds of chromatographed / distilled materials. **3**, E = H (10-20%) were removed in the purification. [b] > 95% d_1 by ^1H NMR.

When the *t*-BuLi addition to the parent carbamate **1**, G = H was followed by PhCHO quench, a diastereoisomeric mixture (3:1 by ^1H NMR) of **8**, the result of a subsequent carbamoyl migration,[1a] was isolated (**Scheme 3**). When the intermediate **9** was refluxed before workup, epoxide **10** was isolated as the sole product. On the assumption of an anti-periplanar OLi - $OCONEt_2$ requirement for epoxide formation, the major product was tentatively assigned the **8**-*anti* (α-$OCONEt_2$) diastereomer. Conformational analysis (SYBYL) of **9** indicates that conformation **11** is favored for the **9**-*anti*

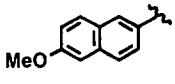
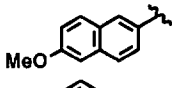
diastereomer which can lead to epoxide **10**. The lowest energy conformation **12** of the **9**-*syn* diastereomer will not lead to epoxide formation. An nOe (22 %) between the CH_2 and CH established the *cis* stereochemistry of **10** giving credence to this calculational result.

Scheme 3



The results of the one-pot carbolithiation - [1,2]-Wittig rearrangement[12] are summarized in **Table 2.** Good yields of 2-aryl propionamides were obtained using *n*-BuLi and *t*-BuLi initiation although yields were compromised in substituted α-aryl cases (entries 3, 6, 7), as perhaps expected, due to addition reactions (entry 3). Naproxen analogues are accessible (entries 4, 8)[13] as are pyridyl acetamides (entries 9, 10), the latter with the same comment as in the α-alkylation sequence (*vide supra*).

Table 2. Tandem β–Carbolithiation - [1,2]-Wittig Rearrangment of α-Aryl *O*-Vinyl Carbamates 1

Entry	RLi[a]	Product **4**		yld, [b] %
		R	Ar	
1	*n*-BuLi	*n*-Bu	Ph	80
2	*n*-BuLi	*n*-Bu	(3-MeO)C_6H_4	75
3	*n*-BuLi	*n*-Bu	(3-Et_2NOC)C_6H_4	25
4	*n*-BuLi	*n*-Bu		74
5	*t*-BuLi	*t*-Bu	Ph	50
6	*t*-BuLi	*t*-Bu	(3-MeO)C_6H_4	46
7	*t*-BuLi	*t*-Bu	(3-Et_2NOC)C_6H_4	55
8	*t*-BuLi	*t*-Bu		73
9	*t*-BuLi	*t*-Bu		66
10	*t*-BuLi	*t*-Bu		65

[a] For *n*-BuLi reactions, TMEDA (1 equiv) was used. [b] See footnote *a*, Table 1.

In summary, α-aryl and -heteroaryl *O*-vinyl carbamates **1** have been shown to be highly receptive substrates for carbolithiation, presumably owing to a CIPE activation. The resulting benzylic anions **2**, stabilized against polymerization,[3] undergo α-alkylaton and/or [1,2]-Wittig rearrangement thus providing synthetic routes to branched benzyl *O*-carbamates **3** and 2-aryl-2-hydroxypropionamides **4**, including pyridyl derivatives, related to the Naproxen/Ibuprofen family of antiinflammatory agents. These findings argue for the broader methodological utility of the reported chemistry.[14-17]

References and Footnotes

† Monsanto Scholar, 1995 - 1996.

1. a) Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990,** *55*, 5680; b) Lee, J.; Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 415; c) Superchi, S.; Sotomayor, N.; Miao, G.; Joseph, B.; Snieckus, V. *Tetrahedron Lett.* accompanying letter in this issue.
2. As may be surmised with a little reflection, this reaction was serendipitous by discovered in attempts to effect directed *ortho* metalation of **1**.
3. Anionic polymerization of styrene and conjugated dienes. See Morton, M. *Anionic Polymerization:Principles and Practice.* Academic Press: New York, 1983.
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8. The β-metalation of α-phenyl-*O*-methoxymethyl vinyl ethers and α-benzotriazolyl-*O*-ethyl vinyl ethers is accompanied by 5-10% of α-carbolithiation products, see McDougal, P. G.; Rico, J. G. *Tetrahedron Lett.* **1984,** *25*, 5977. Katritzky, A.; Ignatchenko, A. V.; Lan, X.-F.; Lang, H.-Y.; Stevens, C. V. *Tetrahedron*, **1994,** *50*, 6005.
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11. Using **1**, G = 3-MeO and excess MeI as the quench led to (3-MeO)$C_6H_4COCHMe_2$ (20%), a result of carbamoyl attack and α-alkylation. The PhLi-TMEDA/MeI combination gave **3**, R = Ph, E = Me in 13% yield while PhMgCl was unreactive.
12. First demonstrated by Hoppe on a benzyl *O*-carbamate prototype, see Hoppe, D. *Angew Chem. Int. Ed. Engl.* **1984,** *23*, 932. See also Zhang, P.-S.; Gawley, R. E. *J. Org. Chem.* **1993,** *58*, 3223; Hoffmann, R.; Brücker, R. *Chem. Ber.* **1992**, *125*, 1957.
13. To the best of our knowledge, Naproxen derivatives corresponding to **4** with R variation have not been described. See ref 10.
14. *Typical Experimental Procedure:* To a stirred solution of TMEDA (0.68 mmol) in anhyd THF (10 mL) at -78 °C under nitrogen was added *t*-BuLi (0.68 mmol, 0.45 mL of a 1.52 M solution) . After 1 h, a solution of **1** in THF (5 mL) was injected dropwise via syringe and the mixture was stirred for 1 h. For product **3**, electrophile (2.04 mmol) was added dropwise; for product **4**, no electrophile was added. The reaction mixture was allowed to warm to rt over 12 h, quenched with satd. NH_4Cl (10 mL), and extracted with ether (20 mL x 3). The combined extract was washed with water, brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was subjected to flash chromatography (hexane/EtOAc as eluent) to afford **3** or **4**.
15. Modest but promising enantioinduction in the (-)-sparteine-mediated carbolithiation - α-alkylation reaction has been recently achieved. Thus, using the above procedure but replacing TMEDA with (-) sparteine (1.1 equiv) and THF by hexane gave the product of entry 1, **Table 1** in 62% yld and 53% ee (HPLC with (*S, S*)-Whelk-O1 column) Miao, G.; Snieckus, V. work in progress.
16. All new compounds show analytical and spectral (^1H, ^{13}C NMR, IR, HRMS) data in accord with the assigned structures.
17. We thank NSERC Canada and Monsanto for support under the Monsanto/NSERC Industrial Research Chair program. MC gratefully acknowledges Monsanto for the Monsanto Scholar Award. SS and NS gratefully acknowledge Universita di Pisa (Italy) and "Gobierno Vasco" (Spain) respectively for fellowships without which this work would not have been achieved.

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