

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

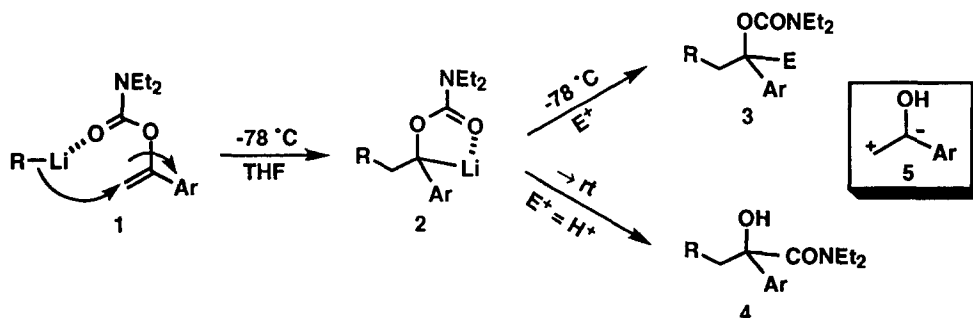
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Abstract: Efficient, one-pot carbolithiation - α -alkylation and -[1,2]-Wittig rearrangement processes of α -aryl *O*-vinyl carbamates **1** to branched benzyl *O*-carbamates **3** and 2-aryl-2-hydroxypropionamides (*mandelic amides*) **4**, including Naproxen analogues, is described. Copyright © 1996 Elsevier Science Ltd

We report on new one-pot tandem carbolithiation – α -alkylation and -[1,2]-Wittig rearrangement regimens of α -aryl *O*-vinyl carbamates **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 alkylolithiums to allylic alcohols⁵ and amines⁶ 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

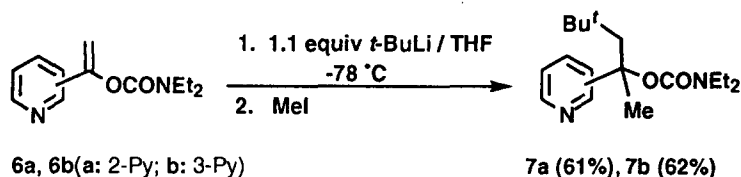
Scheme 1



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). Inadvertently explored² 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

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

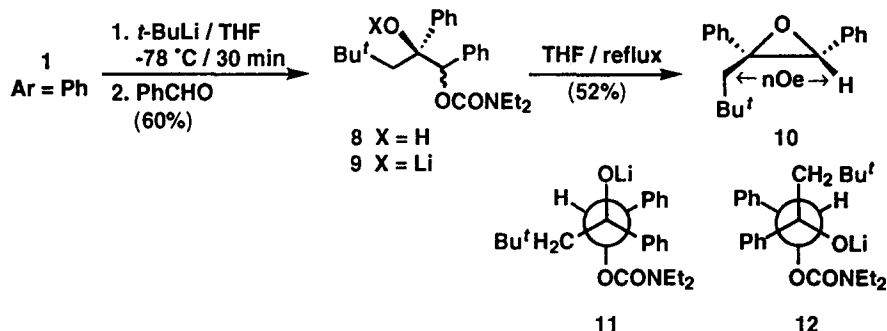
Entry	RLi	E ⁺	Product 3			yld, ^a %
			R	E	Ar	
1	<i>n</i> -BuLi	MeI	<i>n</i> -Bu	Me	Ph	80
2	<i>n</i> -BuLi		<i>n</i> -Bu		Ph	64
3	<i>n</i> -BuLi	PhCH ₂ Br	<i>n</i> -Bu	CH ₂ Ph	Ph	66
4	<i>n</i> -BuLi	TMSCl	<i>n</i> -Bu	TMS	Ph	82
5	<i>s</i> -BuLi	MeI	<i>s</i> -Bu	Me	Ph	80
6	<i>t</i> -BuLi	MeOD	<i>t</i> -Bu	D	Ph	96 ^b
7	<i>t</i> -BuLi	MeI	<i>t</i> -Bu	Me	Ph	90
8	<i>t</i> -BuLi	EtI	<i>t</i> -Bu	Et	Ph	71
9	<i>t</i> -BuLi		<i>t</i> -Bu		Ph	61
10	<i>t</i> -BuLi	PhCH ₂ Br	<i>t</i> -Bu	CH ₂ Ph	Ph	80
11	<i>t</i> -BuLi	MeI	<i>t</i> -Bu	Me	(3-MeO)C ₆ H ₄	78
12	<i>t</i> -BuLi	PhSeCl		(3-MeO)C ₆ H ₄ COCH ₂ Bu ^f		45
13	<i>t</i> -BuLi	MeI	<i>t</i> -Bu	Me	(3-Et ₂ NOC)C ₆ H ₄	50

^a Ylds of chromatographed / distilled materials. 3, E = H (10-20%) were removed in the purification. ^b > 95% d₁ 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 - OCONEt₂ requirement for epoxide formation, the major product was tentatively assigned the **8-anti** (α -OCONEt₂) diastereomer. Conformational analysis (SYBYL) of **9** indicates that conformation **11** is favored for the **9-anti**

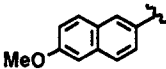
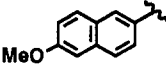


diastereomer which can lead to epoxide **10**. The lowest energy conformation **12** of the 9-*syn* diastereomer will not lead to epoxide formation. An *n*Oe (22 %) between the CH₂ and CH established the *cis* stereochemistry of **10** giving credence to this calculational result.

Scheme 3



The results of the one-pot carbolithiation - [1,2]-Wittig rearrangement¹² 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 Rearrangement of α -Aryl *O*-Vinyl Carbamates **1**

Entry	RLi ^a	Product 4		yld, ^b %
		R	Ar	
1	<i>n</i> -BuLi	<i>n</i> -Bu	Ph	80
2	<i>n</i> -BuLi	<i>n</i> -Bu	(3-MeO)C ₆ H ₄	75
3	<i>n</i> -BuLi	<i>n</i> -Bu	(3-Et ₂ NOC)C ₆ H ₄	25
4	<i>n</i> -BuLi	<i>n</i> -Bu		74
5	<i>t</i> -BuLi	<i>t</i> -Bu	Ph	50
6	<i>t</i> -BuLi	<i>t</i> -Bu	(3-MeO)C ₆ H ₄	46
7	<i>t</i> -BuLi	<i>t</i> -Bu	(3-Et ₂ NOC)C ₆ H ₄	55
8	<i>t</i> -BuLi	<i>t</i> -Bu		73
9	<i>t</i> -BuLi	<i>t</i> -Bu		66
10	<i>t</i> -BuLi	<i>t</i> -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 -alkylation 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**.
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11. Using **1**, G = 3-MeO and excess MeI as the quench led to (3-MeO)C₆H₄COCHMe₂ (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.; Brucker, 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. NH₄Cl (10 mL), and extracted with ether (20 mL x 3). The combined extract was washed with water, brine, dried over MgSO₄ 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, ¹³C 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 Università di Pisa (Italy) and "Gobierno Vasco" (Spain) respectively for fellowships without which this work would not have been achieved.

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