J. Am. Chem. Soc. **1998,** *120,* 4865−4866 4865

First Intramolecular Carbometalation of Lithiated Double Bonds. A New Synthesis of Functionalized Indoles and Dihydropyrroles

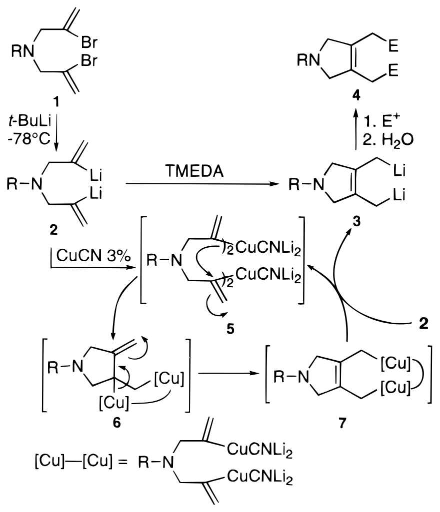
José Barluenga,*,† Roberto Sanz,‡ Alejandro Granados,† and
Francisco J. Fañanás†

Instituto Universitario de Química
Organometálica "Enrique Moles", Unidad Asociada
al C.S.I.C., Universidad de Oviedo
Julián Clavería, 8, E-33071, Oviedo, Spain
Departamento de Química, Área de Química Orgánica,
Facultad de C.yT.A. y CC. Químicas, Universidad de Burgos
Pza. Missael Bañuelos, s/n, E-09001, Burgos, Spain

Received February 20, 1998

Ring-forming reactions of highly reactive carbanions present the potential difficulty that the electrophilic site must tolerate the conditions necessary to form an anion. In this context, inactivated double bonds have been used as internal electrophiles for the addition of alkyl[1] and vinyllithium[2] reagents to afford lithiomethylcyclopentane and methylencyclopentane derivatives, respectively. However, the intramolecular carbolithiation of isolated alkenes is limited to terminal olefins and 1,2-disubstituted alkenes in which the initially formed alkyllithium product is substituted with a leaving group in a β-position[3] or is stabilized by the attachment of a moderately activating group.[4] Recently, 3-substituted indolines have been prepared by easy carbolithiation of 2-(*N*-allylamino)phenyllithium derivatives.[5] However, subsequent oxidation is necessary in order to obtain the corresponding indoles, which are important structures due to the wide range of biological activity found among them.[6] Indole syntheses with formation of the C3−C3a bond are usually carried out by Pd-catalyzed *exo-trig* cyclization of *o*-halo-*N*-allylanilines[7] or *endo-trig* cyclization of *o*-halo-*N*-vinylanilines.[8] However, these methods do not allow the functionalization of the indole ring at the same reaction step. On the other hand, the use of vinylmetals as electrophiles is not usual and only the allylzincation of vinylorganometallics is a general reaction. Nevertheless, this transformation, which affords 1,1-dimetallic species, involves a metala-Claisen rearrangement rather than a carbometalation reaction.[9]

Scheme 1



We have recently reported the intramolecular carbolithiation of *N*-allyl-*N*-(2-lithioallyl)amines that proceeds via 5-*exo* or 6-*endo* depending on the electron density on the nitrogen atom.[10] The easy intramolecular addition of *N*-(2-lithioallyl)amines to simple alkenes prompted us to investigate the addition to a lithium-substituted alkene. In the present paper, we describe the first intramolecular carbometalation of lithiated double bonds promoted by TMEDA or catalyzed by CuCN in organolithium compounds derived from bis(2-bromoallyl)amines or 2-bromo-*N*-(2-bromoallyl)anilines affording functionalized dihydropyrrole or indole derivatives, respectively.

The starting materials chosen to test this possibility were *N*,*N*-bis(2-bromoallyl)amines **1**. Their treatment with 4 equiv of *t*-BuLi in diethyl ether at −78 °C led to the vinyllithium derivatives **2**, which were characterized by deuteriolysis. These dianions were stable in solution but the addition of 4 equiv of TMEDA at low temperature afforded, after the cooling bath was removed and the reaction mixture was allowed to stand at 20 °C, the dilithiated dihydropyrrole derivatives **3**. This transformation involves the cycloisomerization of vinyllithium to allyllithium moieties with formation of a new carbon−carbon double bond. These intermediates **3** were characterized by deuteriolysis or treatment with different electrophiles to give the functionalized heterocycles **4** (Scheme 1 and Table 1).

The formation of dihydropyrrole derivatives **4** could be understood by assuming an intramolecular carbolithiation of one vinyllithium moiety by the other one, which would generate methylenepyrrolidine derivatives of type **6** in which the two metals are lithium. These intermediates could undergo an allylic rearrangement to give dilithiated compunds **3**, which furnish compounds **4** after treatment with electrophiles (Scheme 1).

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† Universidad de Oviedo.

‡ Universidad de Burgos.

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S0002-7863(98)00587-3 CCC: $15.00

Table 1. Dihydropyrrole and Indole Derivatives **4**, **12**, **14**, and **15** from 2-bromoallylamines **1** and **8**

starting amine	R	electrophile	product	yield (%)[a]
1a	PhCH$_2$	D$_2$O	**4a**, E = D	85
1a	PhCH$_2$	Me$_3$SiCl	**4a**, E = SiMe$_3$	82
1a	PhCH$_2$	Bu$_3$SnCl	**4a**, E = SnBu$_3$	79
1b	Ph	D$_2$O	**4b**, E = D	91
1b	Ph	Me$_3$SiCl	**4b**, E = SiMe$_3$	87
1b	Ph	Bu$_3$SnCl	**4b**, E = SnBu$_3$	85
8a	PhCH$_2$	D$_2$O	**12a**, E = D	72
8a	PhCH$_2$	Me$_3$SiCl	**12a**, E = SiMe$_3$	65
8a	PhCH$_2$	(PhCH$_2$S)$_2$	**12a**, E = SCH$_2$Ph	63
8b	Me	D$_2$O	**12b**, E = D	79
8b	Me	Me$_3$SiCl	**12b**, E = SiMe$_3$	68
8b	Me	4-ClC$_6$H$_4$CHO	**12b**, E = 4-ClC$_6$H$_4$CHOH	71
8b	Me	PhCH=NCH(Me)Ph	**12b**, E = PhCHNHCH(Me)Ph	61[b]
8b	Me	E$_1$ = E$_2$ = D$_2$O	**14**, E$_1$ = E$_2$ = D	80
8b	Me	E$_1$ = Me$_3$SiCl, E$_2$ = D$_2$O	**14**, E$_1$ = SiMe$_3$, E$_2$ = D	61
8b	Me	E$_1$−E$_2$ = PhCOCOPh	**15**, R^1 = Ph	47[c]
8b	Me	E$_1$−E$_2$ = MeCOCOMe	**15**, R^1 = Me	42[c]

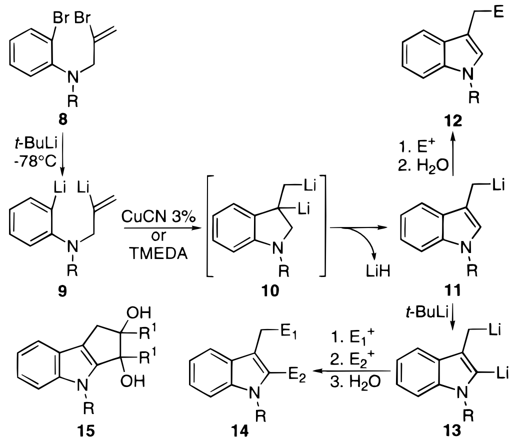
[a] Based on starting amine **1** or **8**. [b] A 6:1 mixture of diastereoisomers was obtained. [c] Only one diastereoisomer was obtained.

Moreover, when the dianions **2** were treated with a catalytic amount of CuCN[11] (3%), they underwent an analogous process and afforded, after quenching with electrophiles, the same dihydropyrrole derivatives **4**. In this case, a reasonable mechanism that accounts for the formation of **3** is outlined in Scheme 1 and involves first a copper−lithium exchange to give the high order cuprate **5**, which undergoes an intramolecular carbocupration of a vinyl moiety affording the dimetallic pyrrolidine derivative **6**. Allylic rearrangement from **6** to **7**, followed by interaction with the dianion **2**, produces the dihydropyrrole derivative **3** with recovery of the active catalytic species **5**. Interestingly, when the reaction was carried out with higher amounts of the copper salt (>20%), the dideuterated diallylamines corresponding to dianions **2** began to appear after deuteriolysis, being the only products when 1 equiv of CuCN was added.

It is interesting to note that carbocupration of isolated double bonds is generally not possible, though some strained alkenes,[12] as well as 1,2- and 1,3-dienes,[13] react with several organocopper reagents. However, we have recently reported that cuprates derived from *N*-allyl-*N*-(2-lithioallyl)amines are able to carbometalate intramolecularly the double bond.[14]

To extend the scope of this new reaction we carried out the process with 2-bromo-*N*-(2-bromoallyl)anilines **8** as starting materials. Bromine−lithium exchange in the same reaction conditions described above afforded the dianions **9** which under treatment with TMEDA or CuCN (3%) underwent intramolecular carbometalation of the vinyllithium moiety by the aryllithium to afford dilithiated indoline derivatives **10**. In this case, since an allylic rearrangement would involve the loss of aromaticity of the aromatic ring, elimination of lithium hydride takes place.[15] In this way, 3-lithiomethylindole derivatives **11** are generated. Compounds **11** can react with different electrophiles to afford functionalized indole derivatives **12**. When benzylidene-α-methylbenzylamine was used as electrophile, a 6:1 diastereoisomeric ratio of the corresponding indoles **12** was obtained (Scheme 2 and Table 1).

Scheme 2



The preparation of *N*-unsubstituted indoles by this intramolecular carbometalation would be of the great interest. Thus, when the reaction was carried out with secondary amine **8** (R = H) the addition of TMEDA causes the evolution of the corresponding trianion **9** (R = Li) to the indole derivative **11** (R = Li). However, the process is slower and decomposition of 3-lithiomethylindole is in competition with the intramolecular carbolithiation. Therefore, after 8 h at room temperature and subsequent deuteriolysis, an equimolecular mixture of **12** (E = D, R = H) and the dideuterated amine corresponding to the intermediate **9** was obtained. However, for a longer reaction time (16 h), the formation of methylindole **12** (R = E = H) in 60% yield was observed. Although it is not possible, in this case, the preparation of different 3-functionalized indoles by the reaction with electrophiles, this procedure would allow the synthesis of *N*-unsubstituted 3-methylindole derivatives. In this case, the addition of CuCN was unsuccessful probably due to the interaction of the copper with the lithium amide.

It is well established that 1-protected-indoles are readily lithiated at C-2 because of the influence of the heteroatom.[16] Therefore, when **8** was treated with 5 equiv of *t*-BuLi, the formation of dilithiated compounds **13** was observed. Their subsequent reaction with two different electrophiles led to 2,3-difunctionalized indole derivatives **14**. Otherwise, the treatment of **13** with 1,2-diketones afforded cyclopent[*b*]indole derivatives **15** as a single diastereoisomer (Scheme 2 and Table 1).

In conclusion, we have described an efficient conversion of dilithiated compounds, derived from bis(2-bromoallyl)amines, to dihydropyrrole derivatives by using TMEDA or catalytic amounts of CuCN, representing, as far as we know, the first intramolecular carbometalation of lithiated double bonds. In addition, a simple and straightforward synthesis of indoles has been also developed on the basis of this strategy. Further studies on the mechanism and synthetic applications of this novel transformation will be reported in due course.

Acknowledgment. This work was supported by DGICYT (Grant PB92-1005). R. Sanz and A. Granados thank the Ministerio de Educación y Ciencia and the CONICET (Argentina), respectively, for fellowships.

Supporting Information Available: Synthetic procedures, spectral data for **4**, **12**, **14**, and **15**, and ^{13}C NMR spectra (24 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

JA9805876

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[11] Same results are observed by using CuI and CuCl instead CuCN.

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