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Parham-Type Cycliacylation with Weinreb Amides. Application to the Synthesis of Fused Indolizinone Systems

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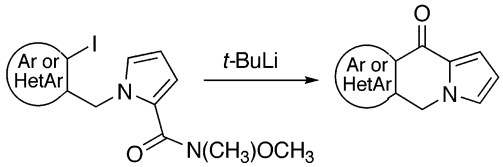
ABSTRACT



Weinreb amides behave as efficient internal electrophiles in Parham-type cycliacylation reactions. Thus, aryl- and heteroaryllithiums generated by lithium–halogen exchange undergo intramolecular cyclization to give fused indolizinone systems as pyrrolo[1,2-*b*]isoquinolines, thieno-[2,3-*f*]indolizinones, and pyrrolo[1,2-*b*]acridinones in high yields.

Aryl- and heteroaryllithium compounds[1] are interesting building blocks in synthetic organic chemistry because by reaction with carbon electrophiles they produce, together with the formation of a carbon−carbon bond, the transference of functionality to the electrophilic reagent, so polyfunctionalized molecules are prepared in one step. Lithium−halogen exchange, though mechanistically controversial,[2] is a particularly useful tactic for the metalation of aromatic substrates because metal−halogen exchange can effectively compete with the organolithium reaction with internal electrophiles. Thus, many carbocyclic and heterocyclic ring systems have been accessed using Parham-type cyclizations, using various types of internal electrophiles.[3] In this context, we had previously shown[4] that iodine−lithium exchange could be performed on *N*-(*o*-iodobenzyl)pyrrole-2-carboxamides, accessing pyrrolo[1,2-*b*]isoquinolones by a Parham-type cyclization using the *N*,*N*-diethylcarbamoyl group as an internal electrophile. However, moderate yields were obtained, and the procedure was limited to aromatic rings activated with donor groups.

With these precedents, we decided to reinvestigate this protocol using Weinreb amide as an internal electrophile. This type of amides has been widely used in synthesis,[5] although their use in Parham cyclizations is scarce. Thus, aryl- and heteroaryllithium compounds have been generated in the presence of this group to give access to benzocyclobutenones,[6] thieno[2,3-*b*]thiophenes,[7] or methylideneindanones.[8] Weinreb amides have also been successfully used as internal electrophiles in cyclization reactions of organo-

(1) (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, 2nd ed.; Pergamon Pres: New York, 1990. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: New York, 2002.

(2) (a) Bailey, W. F.; Patricia, J. I. *J. Organomet. Chem.* **1988**, *352*, 1. (b) Beak, P.; Allen, D. J.; Lee, W. K. *J. Am. Chem. Soc.* **1990**, *112*, 1629. (c) Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420. (d) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 1414. (e) Bailey, W. F. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, 1994; Vol 3. p 251. See also ref 1b.

(3) For reviews, see: (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300 (b) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Exeter, 1995; Vol. 11; p 66. (c) Ardeo, A.; Collado, M. I.; Osante, I.; Ruiz, J.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems Vol. 5*; Atanassi, O., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 2001; p 393. (d) Mealy, M. M.; Bailey, W. F. *J. Organomet. Chem.* **2002**, 649, 59. (e) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 275. See also ref 1

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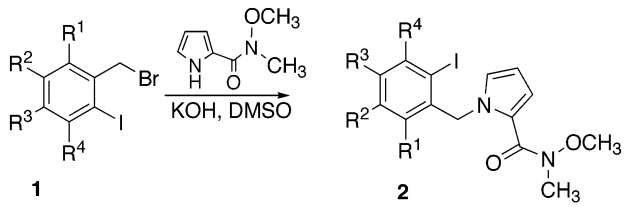
lithiums derived from alkyliodides, accesing cyclic ketones,[9] or vinyliodides, in the synthesis of (−)-brunsvigine[10] or the hexahydrobenzofuran subunit of avermeticin.[11]

N-(*o*-Iodobenzyl) pyrroles **2** were prepared by alkylation of *N*-methoxy-*N*-methylpyrrole-2-carboxamide with benzyl bromides **1a**−**g**[12] under standard conditions (Scheme 1).

Scheme 1

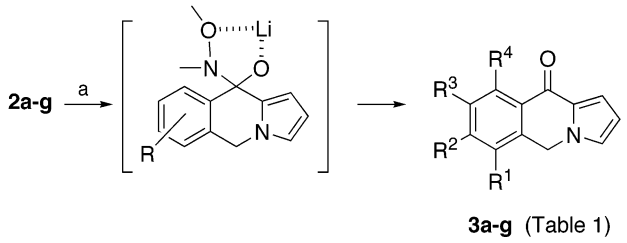


1 **2**

a $R^1 = R^2 = R^3 = R^4 = H$ (90%)
b $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$ (78%)
c $R^1 = R^3 = R^4 = H$; $R^2 = OCH_3$ (83%)
d $R^1 = R^4 = H$; $R^2 = R^3 = OCH_3$ (95%)
e $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$ (61%)
f $R^1 = R^4 = H$; $R^2,R^3 = CH_2OCH_2$ (77%)
g $R^1 = H$; $R^2 = R^3 = R^4 = OCH_3$ (73%)

These benzylpyrroles **2** were submitted to metalation−cyclization conditions using 2.2 equiv of *t*-BuLi at −78 °C (Scheme 2) As shown in Table 1, good yields of pyrrolo-

Scheme 2[a]



3a-g (Table 1)

[a] (a) *t*-BuLi (2.2 equiv), −78 °C.

isoquinolones **3a**−**g** were obtained when the reaction mixture was quenched at low temperature after 3 h (method A). If the reaction mixture was allowed to warm to room temperature before quenching (method B), good yields were also obtained except when the aromatic ring bears methoxy groups on C-6 or C-3 (entries 5 and 7). In these cases, significantly lower yields of cycled products were obtained probably due to an equilibration of the intermediate organolithium prior to cyclization. Besides, a larger excess of *t*-BuLi (3 equiv) was necessary to achieve complete cyclization of benzylpyrrole **2b** (entry 2).

Table 1. Synthesis of Pyrrolo[1,2-*b*]isoquinolines

entry	R	product	method A[a] yield(%)	method B[b] yield(%)
1		**3 a**	87	83 (28)[c]
2	H_3C, H_3C	**3 b**	80[d]	60 (10)[c]
3	CH_3O	**3 c**	69	77 (54)[c]
4	CH_3O, CH_3O	**3 d**	86	70 (79)[c]
5	CH_3O, CH_3O	**3 e**	62	24 (40)[c]
6	O, O	**3 f**	73	72 (34)[c]
7	CH_3O, CH_3O, CH_3O	**3 g**	68	15 (−)[e]

[a] Method A: *t*-BuLi (2.2 equiv), −78 °C, 3 h. [b] Method B: *t*-BuLi (2.2 equiv), −78 °C, 3 h; → rt, 4 h. [c] Yields in parentheses correspond to products obtained using *N*,*N*-diethylamides (see ref 4). [d] 3 equiv of *t*-BuLi was used. [e] No cyclization product was obtained. 81% of deiodinated benzylpyrrole was isolated.

As shown in Table 1, in all cases, the use of Weinreb amides as internal electrophiles improved our previous results in the synthesis of pyrrolo[1,2-*b*]isoquinolones (yields in parentheses). Amides are generally useful electrophiles in Parham cyclizations due to a complex induced proximity effect (CIPE).[13] Thus, lithium−iodine exchange could be favored first by coordination of the organolithium to the amide group and second by stabilization of the resulting aryllithium. The better behavior of Weinreb amides as internal electrophiles in these cyclizations compared to *N*,*N*-diethylamides could be attributed to the extra stabilization

(5) For a review, see: (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. For some more recent examples, see, for instance: (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216. (c) Alberola, A.; González Ortega, A.; Sádaba, M. L.; Sañudo, C. *Tetrahedron* **1999**, *55*, 6555. (d) Alberola, A.; Álvaro, R.; González Ortega, A.; Sádaba, M. L.; Sañudo, C. *Tetrahedron* **1999**, *55*, 13211. (e) Satyamurthi, N.; Singh, J.; Aidhen, I. S. *Synthesis* **2000**, 375.(f) Wang, X.-J.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107. (g) Suh, Y.-G.; Jung, J.-K.; Seo, S.-Y.; Min, K.-H.; Shin, D.-Y.; Lee, Y.-S.; Park, O.-H. *J. Org. Chem.* **2002**, *67*, 1691.

(6) Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.

(7) Selnick, H. G.; Radzilowski, E. M.; Ponticello, G. S. *Tetrahedron Lett.* **1991**, *32*, 721.

(8) Hinkley, S. F. R.; Perry, N. B.; Weavers, R. T. *Tetrahedron Lett.* **1994**, *35*, 3775.

(9) Souchet, M.; Clark, R. D. *Synlett* **1990**, 151.

(10) Sha, C.-K.; Hong, A.-W.; Huang, C.-M. *Org. Lett.* **2001**, *3*, 2177.

(11) Sha, C.-K.; Huang, S.-J.; Zhan, Z.-P *J. Org. Chem.* **2002**, *67*, 831.

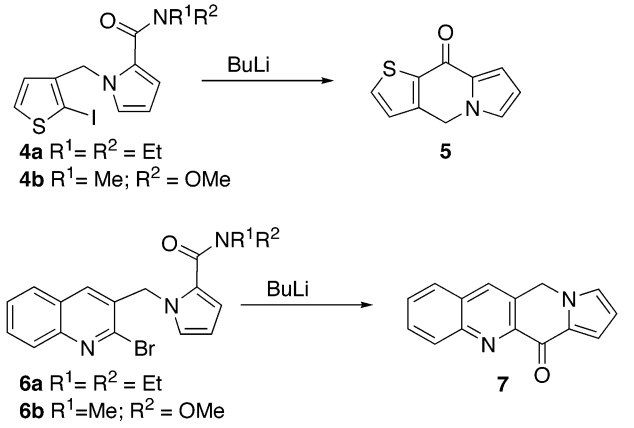
(12) Iodobenzyl bromides **1** were prepared from the corresponding benzylic alcohols in two steps. Aromatic iodination of benzylic alcohols was carried out with I_2/CF_3CO_2Ag in $CHCl_3$ (Janssen, D. E.; Wilson, C. V. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 547) and was completely regioselective in all cases except **e**, where a minor amount of 5-iodo regioisomer was obtained. Subsequent bromination was accomplished PBr_3 in $CHCl_2$ for cases **a**−**f** (Charlton, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490), or with HBr (45%) for case **f**. For representative experimental procedures and characterization data, see the Supporting Information.

(13) This concept has been invoked to explain the enhancement of metalation in hydrogen−metal, metal−metal (Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356), or halogen−metal exchanges (Beak, P.; Musick, T.; Liu, C.; Cooper, T.; Gallagher, D. J. *J. Org. Chem.* **1993**, *58*, 7330).

of the intermediate generated after cyclization by formation of an internal chelate (Scheme 2).

To extend the scope of this Parham-type cycliacylation, we tested the feasibility of using heteroaryllithium compounds to access various fused indolizidinone skeletons. For this purpose, we chose thiophene and quinoline ring systems that incorporated *N*,*N*-diethylamido and *N*-methoxy-*N*-methylamido groups as internal electrophiles. Thus, tenylpyrroles **4a**,**b** and quinolinylmethylpyrroles **6a**,**b** were prepared by standard procedures and submitted to Parham conditions (Scheme 3). As indicated above, two sets of experiments

Scheme 3



were carried out. Heteroaryllithiums were generated with *t*-BuLi (2.2 equiv) at − 78 °C and the reaction quenched at low temperature (method A) or allowed to warm before quenching (method B). Results are summarized in Table 2. As shown for benzylpyrroles, in these substrates the *N*-methyl-*N*-methoxycarbamoyl group turned out to be more efficient internal electrophile than the *N*,*N*-diethylcarbamoyl group in the metalation−cyclization sequence. Thus better yields of thieno[3,2-*f*]indolizinone **5** and pyrroloacridinone **7** were obtained from **4b** and **6b**, respectively (entries 2 and 4). Besides, in both cases cyclization occurred more efficiently when the reaction was quenched at low temperature (method A vs method B). No cyclization products were obtained when heteroaryllithiums derived from **4a** and **6a** were allowed to reach rt. In the case of quinolinylmethylpyrroles **6a,b**, decomposition was observed when treated with *t*-BuLi at −78 °C, and only a low yield of **7** was

Table 2. Synthesis of Fused Indolizidinones

entry	substrate	product	method A[a] yield (%)	method B[b] yield (%)
1	**4a**	5	42[d]	*c*,*d*
2	**4b**	5	71	49
3	**6a**	7	28[e]	*f*
4	**6b**	7	61[e]	20

[a] Method A: *t*-BuLi (2.2 equiv), −78 °C, 6 h. [b] Method B: *t*-BuLi (2.2 equiv), −78 °C, 6 h; → rt. [c] No cyclization product was obtained. 88% of deiodinated tenylpyrrole was isolated. [d] 3 equiv of *t*-BuLi was used. [e] *n*-BuLi (2.2 equiv), −90 °C, 5 min. [f] No cyclization product was obtained. Deiodinated quinolinylmethylpyrrole was isolated (23%).

obtained from **6b**. However, cyclization of **6b** took place rapidly and efficiently when the heteroaryllithium was generated with *n*-BuLi at lower temperature and for a shorter period of time (−90 °C, 5 min) (entry 4).

In summary, it has been shown that *N*-(*o*-iodobenzyl)-pyrrole-2-carboxyamides tolerate lithium−iodine exchange reaction conditions, allowing the efficient construction of the indolizinone nucleus. The *N*-methoxy-*N*-methylcarbamoyl group behaves as an excellent internal electrophile, improving the results obtained with other amides. This procedure has also been extended to heteroaryllithums, opening a new route to heterocyclic systems with potential pharmacological properties that could compete with previously reported strategies.[14]

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Supporting Information Available: Experimental procedures and characterization data of compounds **1d**, **2d**, **3a**−**g**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Pyrrolo[1, 2-*b*]isoquinolines have been synthesized by (a) addition of ortho-lithiated benzamides to the carbonyl group of the *N*-benzylpyrrole-2-carbaldehyde: Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955. (b) Cyclisation of amidyl radicals derived from *O*-acylhydroxamic acid derivatives: Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Synlett* **1999**, 441. (c) Photocyclization of 1-benzyl-1-pyrrolinium salts: Cho, I.-S.; Tu, C.-L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 3594. (d) Thieno[3,2-*f*]indolizinones have been prepared by classical Friedel−Crafts acylation: Decroix, B.; Morel, J. *J. Heterocycl. Chem.* **1991**, *28*, 81.