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Reaction of Carbon Monoxide with *N*-Lithioketimines Derived by the Addition of Alkyllithium to *ortho*-Substituted Benzonitriles. Diverse Courses of Cyclization via Carbonyl Anions

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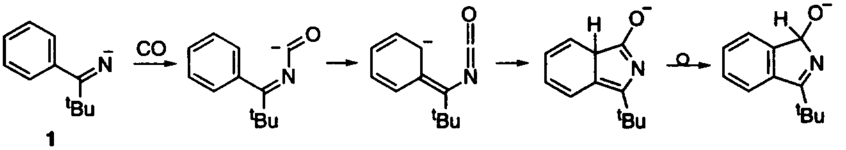
Abstract: *N*-Lithioketimines, generated *in situ* from 2-substituted benzonitriles and t-BuLi, reacted with carbon monoxide to afford five-, six- or seven-membered cyclic products, involving participation by the *ortho* substituents. The reactions represent new selective transformations of carbonyllithium intermediate which previously were observed to lead to complicated reactions.

It is well known that organolithium compounds react with carbon monoxide, generating carbonyllithium derivatives as initial intermediates. The carbonyllithium is generally too reactive to undergo selective reactions, but this can be overcome by trapping carbonyllithium *in situ* with electrophiles as has been reported by Seyferth[1] and others.[2] In this laboratory, we have been studying methodology for the intramolecular conversion of carbonyllithium into more stable and useful species, such as enolates[3,4] or a ynolate which would be useful as a ketenylating reagent.[3e]

In a previous paper, we reported that the reaction of an *N*-lithioketimine, generated from benzonitrile and t-BuLi, with carbon monoxide underwent a selective cyclization to give a 1*H*-isoindole derivative after quenching with MeI (eq 1).[3c] The cyclization took place at the *ortho* position via *N*-lithioketimine **1**.



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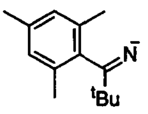
(1)

This type of cyclization appears to be general since *p*-tolunitrile and *p*-methoxybenzonitrile react in a similar manner.[3c] However, when 2,4,6-trimethylbenzonitrile was used in place of benzonitrile, a cyclization reaction did not take place, and instead, undesired reactions were observed.[3c] This may be due to the difficulty of t-BuLi in attacking the cyano group to give **2** as the result of steric hindrance. Even if **2** is formed, coplanarity cannot be attained in **3** and, as a result, the *ortho* carbon atom positions in **3** are at some distance from the carbonyl anion thus making a cyclization reaction difficult or impossible. Because of this, a series of experiments has been carried out to study the course of mono-substituted phenyl derivatives, such as **4**. In the course of **4**, the *ortho* position and the carbonyl anion are sufficiently close to one another to react. Moreover, the rotational isomer **5** must be unstable due to steric repulsion by the *ortho* substituent. Thus, any reaction must take place at the side of the substituted *ortho* position, i.e., interestingly, the more crowded site via **4**. We examined the reaction of carbonyl anion **4**, derived from t-BuLi with benzonitriles having various substituents at the *ortho* position. As a result of this, a novel and interesting series of reaction of carbonyl anions have been discovered.



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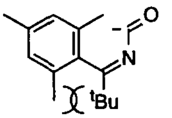

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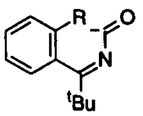

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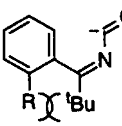

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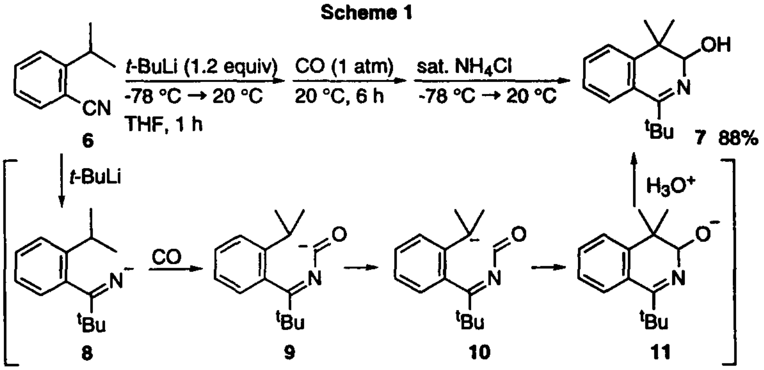
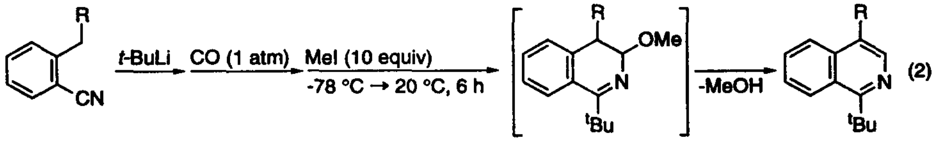
A new type of cyclization has been observed for 2-isopropylbenzonitrile **6**. The reaction of **6** with t-BuLi (1.2 equiv) in THF was carried out for 1 h, initially at -78 °C with gradual warming to 20 °C, followed by exposure to carbon monoxide at 1 atm for 6 h, and quenching with aqueous NH_4Cl. The reaction was very clean and gave a single product, 4,4-dimethyl-1-(1,1-dimethylethyl)-3,4-dihydroisoquinolin-3-ol (**7**), in 88% yield (Scheme 1).[5] Interestingly, this reaction proceeded via an intramolecular benzylic hydrogen transfer in the carbonyl anion intermediate **9** to give the benzyl anion **10**, which then underwent cyclization to give a six-membered product **11**. This process seems to be more favorable than that for five-membered ring formation, such that shown in eq 1 and due to the preservation of aromaticity in the benzene ring in every step. In this reaction, the benzylic hydrogen can be regarded as an intramolecular electrophile which serves to trap the carbonyl anion intermediate **9**.[6] A similar intermolecular protonation of acyllithium was reported in the reaction of alkyllithium with carbon monoxide at low temperature in the presence of CH_3CN[2b] or $CHCl_2R$ (R=H, Ar)[2c] as proton sources. These reactions also involve the generation of a formyl group by protonation and the successive reaction with a concomitantly generated anion ($LiCH_2CN$, $LiCCl_2R$) to produce an alkoxy anion.

Scheme 1

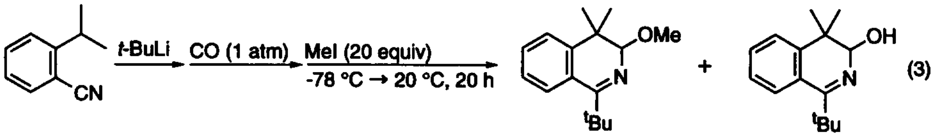


A similar cyclization was also observed for 2-methylbenzonitrile and 2-ethylbenzonitrile. Both reactions gave isoquinoline derivatives **13**[7] in 68% and 82%, respectively, on quenching with methyl iodide (eq 2). These products would be predicted to arise by the elimination of MeOH from **12**. When the reaction of *N*-lithioketimine **8** with carbon monoxide was quenched with MeI (20 equiv) at -78 °C then allowed to further react at 20 °C for 20 h, the corresponding methyl ether **14**[7] was obtained in 61% along with **7** in 22% (eq 3). This provides support for the intermediacy of methyl ether **12** in the formation of isoquinolines **13**.



12

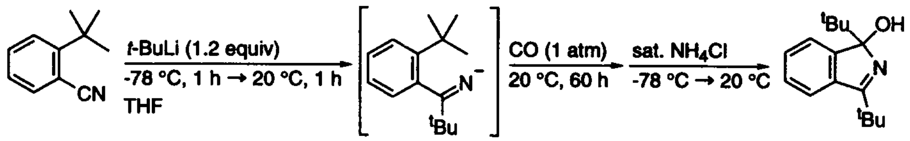
13 a: R=H 68%
b: R=Me 82%



(3)

6 **14** 61% **7** 22%

In order to study the reaction of a benzonitrile derivative, which contains no benzylic hydrogen, we examined the reaction of 2-*tert*-butylbenzonitrile. The *N*-lithioketimine **15** could be easily generated in an analogous manner.[8] However, the reaction with carbon monoxide proceeded very slowly. When this reaction was quenched with aqueous NH_4Cl solution after 60 h, 1,3-bis(1,1-dimethylethyl)-1*H*-isoindol-1-ol (**16**)[7,9] was obtained in only 21% yield, along with the protonated compound derived from **15** in 70% yield (eq 4). The formation of **16** follows the same cyclization course as eq 1 but with migration of the t-Bu group. It is quite interesting that the sterically more crowded *ortho* position is the center of the reaction and provides support for our scenario for the formation of **4** and **5**.

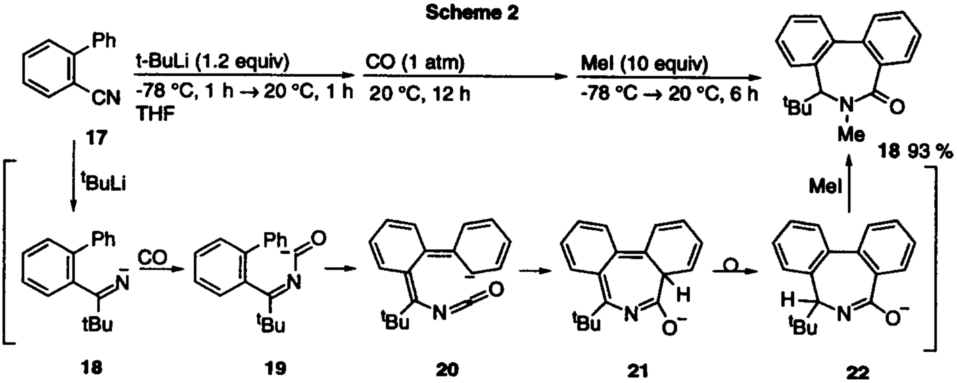


(4)

15 **16** 21%

Interestingly, the reaction of 2-phenylbenzonitrile (**17**), another benzonitrile which contains no benzylic hydrogen, proceeded quite differently. The *N*-lithioketimine **19** was generated *in situ* from (**17**) and t-BuLi, and then reacted with an atmospheric pressure of carbon monoxide followed by quenching with MeI (10 equiv). The product was a seven-membered lactam, 7-(1,1-dimethyethyl)-6-methyl-6,7-dihydro-5*H*-dibenz[c,e]azepine-5-one (**18**),[7] isolated in 93% yield after column chromatography on silica gel (Scheme 2). The carbonyl anion intermediate **20** would undergo cyclization from the anionic isocyanate **21** to a seven-membered ring **22** followed by [1,5] hydrogen shift with aromatization, leading to **23**. This reaction can be regarded as formal [6+1] cyclocoupling reaction involving the participation of the two double bonds in the aryl groups. No five-membered ring products, obtainable via eq 1 were observed.

Scheme 2



In summary, we have reported some new selective reactions via carbonyl anions in the reactions of carbon monoxide with *N*-lithioketimines prepared from 2-substituted benzonitriles with t-BuLi. A diversity of reaction pathways exist and these would be controlled by steric and electronic feature of the *ortho* substituent. The cyclization is attained in various ways such as alkyl migration, benzylic hydrogen abstraction, and formal [6+1] cyclocoupling.

Acknowledgment This work was supported, in part, by grants from Monbusho.

References and Notes

1. (a) For representative examples, see: Seyferth, D.; Weinstein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534. (b) Seyferth, D.; Hui, R. C.; Wang, W. -L.; Archer, C. M. *J. Org. Chem.* **1993**, *58*, 5843 and references cited therein.
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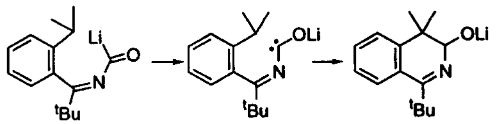
4. Smith, K.; Pritchard, G. J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 282.
5. In a typical experiment, a 50-mL round-bottomed flask, equipped with a magnetic stirring bar, a three-way stopcock, and a nitrogen line was flame-dried under a stream of nitrogen. In the reaction flask were placed 10 mL of anhydrous THF and 290 mg (2 mmol) of **6**, and the solution was cooled to -78 °C with a dry-ice/MeOH bath. To the stirred solution, 1.5 mL of a pentane solution of t-BuLi (1.6 M, 2.4 mmol) was added dropwise by a syringe, and the mixture was allowed to gradually warm to 20 °C with continued stirring over a 1 h period. The three-way stopcock was then connected to a vacuum line (10 mmHg) and also to a balloon filled with carbon monoxide through a glass column packed with anhydrous calcium chloride and anhydrous calcium sulfate. After two cycles of evacuation of nitrogen and filling with carbon monoxide, the reaction mixture was stirred under the atmosphere of carbon monoxide for 6 h at 20 °C. During this period 60 mL (1.25 equiv) of carbon monoxide was absorbed. The reaction mixture was then quenched with aqueous NH_4Cl at -78 °C and allowed to gradually warm to 20 °C. After the usual workup, 1-(1,1-dimethylethyl)-4,4-dimethyl-3,4-dihydroisoquinolin-3-ol (**7**) was obtained in 88% yield by means of column chromatography on silica gel (hexane/EtOAc = 10/1, R_f = 0.19). Colorless solid: ^1H NMR ($CDCl_3$, 270 MHz) δ 0.96 (s, 3H), 1.40 (s, 9H), 1.44 (s, 3H), 2.3-2.8 (bs, OH), 4.67 (s, 1H), 7.2-7.3 (m, 1H), 7.32-7.46 (c, 2H), 7.78 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 19.1, 23.1, 29.9, 37.5, 39.0, 88.1, 124.6, 125.4, 126.7, 127.1, 130.4, 147.6, 170.9; IR (KBr) 3276, 1614 cm^{-1} ; MS, *m/z* (relative intensity) 231 (M^+, 47); exact mass calcd for $C_{15}H_{21}NO$: 231.1624, found 231.1640.
6. We cannot rule out lithioxycarbene **9'** as an alternative intermediate which could insert into the benzyl C-H bond to afford **11**. (a) A lithioxycarbene intermediate has been proposed in the reaction of lithium amide with carbon monoxide, see: Viruela-Martin, P.; Viruela-Martin, R.; Tomás, F.; Nudelmann, N. S. *J. Am. Chem. Soc.* **1994**, *116*, 10110.

   (b) The siloxycarbene intermediate, which is the silicon analogue of lithioxycarbene, was reported to undergo intramolecular C-H bond insertion, see: Bassindale, A. R.; Brook, A. G.; Harris, J. *J. Organomet. Chem.* **1975**, *90*, C6. Ando, W.; Sekiguchi, A. *J. Organomet. Chem.* **1977**, *133*, 219.



9 **9'** **11**

7. The compounds were characterized by NMR, IR, mass spectral data and elemental analysis or high resolution mass spectra.
8. The described *N*-lithioketimines were generally prepared in the range of 80-95% yield as confirmed by quenching with MeI.
9. A similar t-Bu group migration was observed, see ref 3c and 4.

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