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Preparation of Trifluoromethyl Lactol Derivatives via Base Initiated Cyclobutanol Ring Opening to a Laterally Lithiated Trifluoromethyl Ketone

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Preparation of Trifluoromethyl Lactol Derivatives via Base-Initiated Cyclobutanol Ring-Opening to a Laterally-Lithiated Trifluoromethyl Ketone

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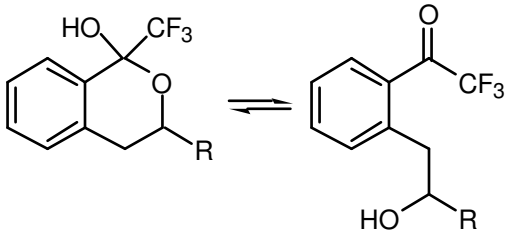
Abstract: Benzocyclobutenone derivatives **4** are converted to the corresponding trifluoromethylcyclobutanols **5** by treatment with trifluoromethyltrimethylsilane in the presence of tetra-n-butylammonium fluoride. These trifluoromethylcyclobutanol derivatives are then treated with LiTMP in the presence of aromatic aldehydes to afford trifluoromethyllactols **6** via a laterally-lithiated trifluoromethylketone intermediate.

Heteroatom-facilitated lateral lithiation[1] of alkyl-substituted aromatic systems is an efficient method for the functionalization of benzylic sites. Lateral lithiation is related to the exceptionally useful method of *ortho* lithiation.[2] We were interested in the preparation of functionalized dihydroisocoumarin trifluoromethyl lactols **1A** because of their equilibrium relationship[3] with the corresponding ortho-substituted trifluoromethyl ketones **1B**, as trifluoromethyl ketones are of great pharmaceutical interest as transition-state esterase and protease inhibitors,[4] and dihydroisocoumarins are a class of naturally occurring lactones which display a wide variety of biological activities.[5]

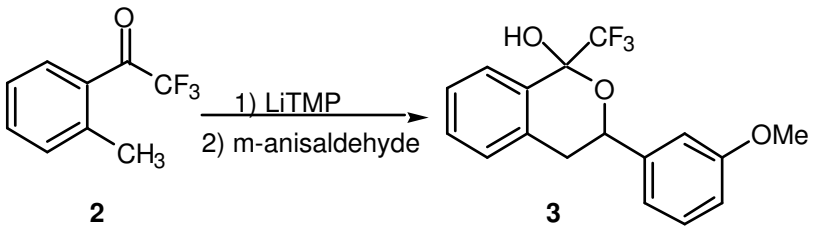


1A **1B**

Dihydroisocoumarins have been successfully prepared utilizing the lateral lithiation methodology from ortho-toluamides,[6] ortho-toluic acids,[7] ortho-toluic esters,[8] and o-tolyl-oxazolines.[9] Our initial attempts to prepare trifluoromethyl lactols focused on the direct deprotonation of 2-methyl-trifluoromethyl acteophenone. The only lateral lithiation of a non-enolizable ketone in the literature to date is by Suginome,[10] who reported the lateral lithiation of tert-butyl-o-tolyl

ketone with LDA followed by treatment with various electrophiles including aldehydes and ketones giving rise to lactols. Attempts to utilize Suginome's conditions employing 2-methyl-trifluoromethylacteophenone **2** to prepare trifluoromethyl lactols did not give detectable amounts of desired lactol product. However, upon switching to the more hindered amide base LiTMP the desired lactol **3** was isolated in 7 % yield. We were encouraged by this result despite the low yield, since it did serve to illustrate that lateral lithiations are feasible with trifluoromethyl ketones.

We then considered alternatives to the direct deprotonation of 2-methyl-trifluoromethylacteophenone **2** in order to improve the yield of derivatives of general type **3**. As trifluoromethyl ketones are more like

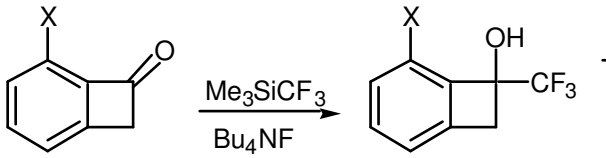


2 **3**

aldehydes in terms of carbonyl electrophilicity, we examined methods of lateral lithiation which have proven to be successful with aldehydes. The method of Comins[11] involves the in situ preparation of an α-amino alkoxide adduct of the aldehyde with the lithium amide of N,N,N'-trimethylethylenediamine. More recently, Flippin[12] has reported the lateral lithiation of the N-cyclohexylimine of o-tolualdehyde. These methods may hold promise for the lateral lithiation of trifluoromethyl ketones, although our preliminary attempts with these methods were unsuccessful.

Olofson[13] has recently described the use of benzocyclobutenols as surrogates for o-tolualdehyde anions in reactions with benzaldehyde derivatives to afford lactols (benzodihydropyranols) which were subsequently oxidized to afford the corresponding dihydroisocoumarins. We wondered if we could utilize trifluoromethyl benzocyclobutenols as surrogates for o-tolyl trifluoromethyl ketone anions. To test this hypothesis we first desired the corresponding benzocyclobutenones which we hoped could serve as intermediates to the trifluoromethyl benzocyclobutenols. We prepared benzocyclobutenones **4a**, **4b**, and **4c** via the benzyne methodology of Stevens[14] and improved by Liebeskind.[15] 1-Trifluoromethyl cyclobutan-1-ols have not been reported before in the literature, but we found that application of Olah's nucleophilic trifluoromethylation procedure[16] utilizing Rupport's[17] reagent gave the

desired trifluoromethyl cyclobutanols **5a**, **5b**, and **5c** consistently in 54-59% yield.

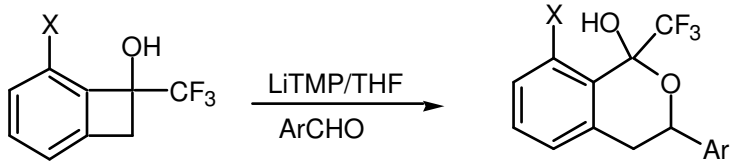


Entry	X	Yield
a	F	59%
b	Cl	59%
c	OMe	54%

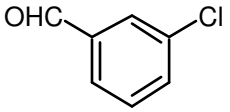
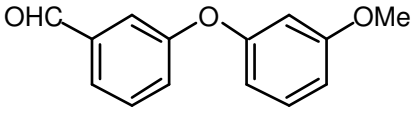
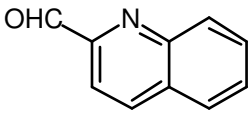
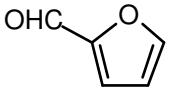
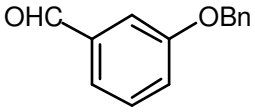
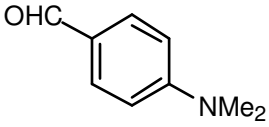
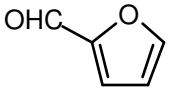
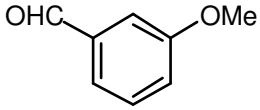
4a-c **5a-c**

With the trifluoromethyl carbinols in hand, we turned our attention to the base-initiated cyclobutanol ring-opening. We were quite pleased to find that treatment of the trifluoromethyl benzocyclobutenols **5** with LiTMP in the presence of aromatic aldehydes did indeed produce the desired trifluoromethyl lactols **6** (Table 1). Utilization of fluoro

Table 1



5a-c **6**

Entry	X	ArCHO	% Yield
1	F		73
2	F		73
3	F		5
4	F		27
5	Cl		57
6	Cl		9
7	Cl		24
8	OMe		51

derivative **5a** with meta-chloro benzaldehyde or meta-(3-methoxyphenoxy)benzaldehyde gave the desired adducts in 73% yield (entries 1 and 2). The utilization of heteroaromatic aldehydes was also successful, although the yields were much lower. Reaction with 2-quinoline carboxaldehyde (entry 3) gave the desired trifluoromethyl lactol in only 5% yield, which may have been due to direct carbanion addition to this electron-deficient heteroaromatic. Utilization of 2-furfural with trifluoromethyl benzocyclobutenol **5a** (entry 4) gave the desired adduct in a modest 27 % yield. Employment of chlorobenzocyclobutanone **5b** gave the desired adduct with m-(benzyloxy)benzaldehyde in 57% yield (entry 5). Reaction of **5b** with p-dimethylaminobenzaldehyde gave the corresponding adduct **6** in only 9% yield (entry 6), whereas 2-furfural gave the desired lactol in 24% yield (entry 7), which is consistent with the result employing **5a** (entry 4). Employment of the methoxy benzocyclobutanone **5c** with

m-anisaldehyde proceeded without incident to afford the desired adduct in 51% yield (entry 8).

The low yields observed with 2-furfural and p-dimethylaminobenzaldehyde may be due to instability of the product lactols. The electron-rich π-systems of the furan and aniline may induce an acid-catalyzed elimination of water from the lactol, giving rise to formation of the free trifluoromethyl ketones and reactive oxonium or iminium ion functionalities, respectively (Figure 1).

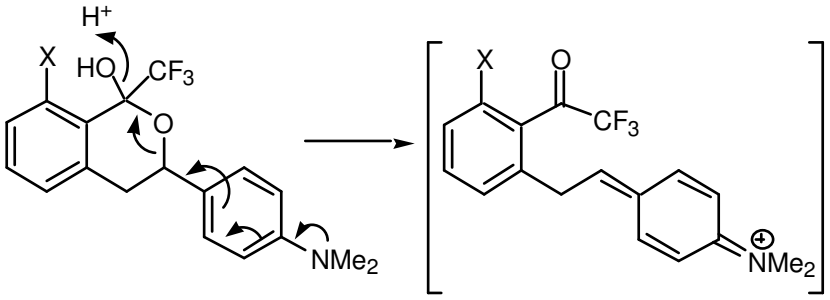


Figure 1

An attempt to react methoxybenzocyclobutanone **5c** with a ketone, 4-fluorobenzophenone, under the same conditions gave several products from which we could not isolate the desired 3,3-disubstituted trifluoromethyl lactol. Laterally lithiated o-toluamides and other laterally lithiated species have been successfully reacted with imines,[18] but reaction of methoxybenzocyclobutanone **5c** with N-benzylidene methylamine under the above conditions did not lead to the isolation of the desired product. The expected product from the reaction with imines may suffer from instability similar to that described in Figure 1 above.

In summary, 1-trifluoromethylcyclobutenols were utilized as surrogates for laterally-lithiated o-tolyl trifluoromethylacetophenone (TFK) derivatives for the preparation of 1-trifluoromethyl lactols. The yields of this transformation were highly dependent upon the structure of the aromatic aldehyde employed. The requisite 1-trifluoromethyl cyclobutenols were been prepared directly from the corresponding benzocyclobutenone derivatives utilizing trifluoromethyltrimethylsilane and fluoride ion catalysis.

*Typical experimental procedure[19] for the preparation of trifluoromethylbenzocyclobutenols **5** from benzocyclobutenones **4**, described for **5a**:* To a solution of cyclobutenone **4a** (288 mg, 2.12 mmol) in dry THF (5 mL) at 0 °C was added trifluoromethyltrimethylsilane (0.44 mL, 3.0 mmol) followed by tetra-*n*-butylammonium fluoride (5 mg, 0.02 mmol). The solution was then allowed to warm to rt. After stirring for 4 h at rt, 1 N HCl (15 mL) was added along with additional THF (2 mL), and the resulting two-

phase solution was stirred vigorously for 1.5 h. Extractive workup (Et_2O) afforded a light brown oil which was chromatographed on silica gel eluting with 10/90 EA/hexane to give the desired trifluoromethylcyclobutanol **5a** (258 mg, 59%) as a colorless oil.

Typical experimental procedure[19] *for the preparation of trifluoromethyl lactols* ***6*** *from trifluoromethylbenzocyclobutenols* ***5****, described for Entry 1:* To a solution of LiTMP [0.23 mmol, prepared from 2,2,6,6-tetramethylpiperidine (33 mg, 0.24 mmol) and n-BuLi (0.14 mL of a 1.6 M solution in hexane, 0.23 mmol] in dry THF at -78°C was added a solution of trifluoromethylcyclobutanol **5a** and 3-chlorobenzaldehyde in THF (0.5 mL). The reaction was allowed to warm to rt over 1 h and then stirred for 16 h at rt. An extractive workup (EA) gave a colorless oil (50 mg) which was purified by preparative thin-layer chromatography to afford the title compound of Entry 1, Table 1 (44 mg, 73%) as a colorless oil.

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References and Notes

1) For an excellent review of ortho lithiation see Clark, R.D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.
2) a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. b) Gschwend, H.W.; Rodriguez, G.R. *Org. React.* **1979**, *26*, 1
3) The strong electron-withdrawing nature of the trifluoromethyl group forces the equilibrium to lie on the side of the cyclic trifluoromethyl lactol. The equilibrium is also under the influence of other structural features, such as lactol ring size.
4) a) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123. b) Begue, J.-P.; Delpon, D. B. *Tetrahedron* **1991**, *47*, 3207.
5) Hill, R.A.; Krebs, H.Chr.; Verpoorte, R.; Wijnsma, R. *Prog. Chem. Org. Nat. Prod.* **1986**, *49*, 1-78.
6) a) Sibi, M.P.; Jalil Miah, M.A.; Snieckus, V. *J. Org. Chem.* **1984**, *9*, 737. b) Vaulx, R.L.; Puterbaugh, W.H.; Hauser, C.R., *J. Org. Chem.* **1964**, *29*, 3514. c) Watanabe, M.; Sahara, M.; Dubo, M; Furukawa, S.; Biledeau, R.F.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 742. d) Comins, D.L.; Brown, J.D. *J. Org. Chem.* **1986**, *51*, 3566.
7) Creger, P.L.; *J. Am. Chem. Soc.* **1970**, *92*, 1396.
8) a) Kraus, G.A. *J. Org. Chem.* **1981**, *46*, 201. b) Regan, A.C.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1983**, 764. c) Carpenter, T.A.; Evans, G.E.; Leeper, F.J.; Staunton, J.; Wilkinson, M.R., *J. Chem. Soc., Chem. Commun.* **1985**, 1258. d) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635.

9) Fu, P.F.; Unruh, L.E.; Miller, D.W.; Huang, L.W.; Yang, D.T.C. *J. Org. Chem.* **1985**, *50*, 1259.
10) Kobayashi, K.; Konishi, A.; Kanno, Y.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 111.
11) Comins, D.L.; Brown, J.D. *J. Org. Chem.* **1984**, *49*, 1078.
12) Flippin, L.A.; Muchowski, J.M.; Carter, D.S., *J. Org. Chem.* **1993**, *58*, 2463.
13) Fitzgerald, J.J.; Pagano, A.R.; Sakoda, V.M.; Olofson, R.A., *J. Org. Chem.* **1994**, *59*, 4117.
14) Stevens, R.V.; Bisacchi, G.S. *J. Org. Chem.* **1982**, *47*, 2393.
15) Liebeskind, L.S.; Lescosky, L.J.; McSwain, C.M. *J. Org. Chem.* **1989**, *54*, 1435. An excellent method for the preparation of benzocyclobutanones via [2+2] cycloaddition of benzynes and ketene silyl acetals followed by acetal hydrolysis has recently been described: Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett.* **1995**, 177.
16) Prakash, G.K.S.; Krishnamurti, R.; Olah, G.A. *J. Am. Chem. Soc.* **1989**, *111*, 393.
17) Rupport, I.; Schlich, K.; Volbach, W. *Tet. Lett.* **1984**, 2195.
18) See, for example Clark, R.D.; Jahangir, A., *J. Org. Chem.*, **1987**, *52*, 5378.
19) All new compounds were fully characterized by ^{1}H-, ^{13}C- and ^{19}F-NMR, IR and HRMS and/or combustion analysis.