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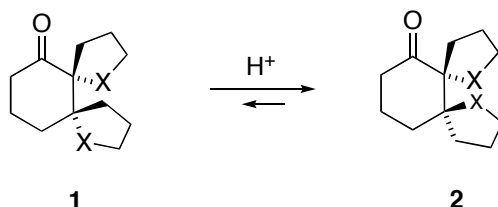
DIRECT ACCESS TO HETEROPOLYCYCLIC SPIROKETONES. 1,3-DICHLOROACETONE AS A CYCLOPROPANONE EQUIVALENT[‡]

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Abstract – A series of hetero spiro cyclobutanones, cyclopentanones, and cyclohexanones has been prepared by taking advantage of the flexibility offered by 1,3-dichloroacetone as a substitute for the elusive cyclopropanone reagent.

It has been previously established in these laboratories that 2,3-dispiro cyclohexanones exemplified by **1** and **2** are amenable to acid-catalyzed interconversion.² Although it proved possible to demonstrate that stereochemical equilibration operates in those systems where X = O or S (both matched and unmatched),³ the synthetic pathway available at that time involved cyclobutanone as the central building block, thereby limiting the core framework to a disubstituted six-membered ketone.⁴ In order to augment our knowledge of this compound class, we have explored the possibility of varying not only the magnitude of the central ring, but the number of spirocycles attached thereto and their individual size. These objectives have been realized by employing 1,3-dichloroacetone (**3**) as a cyclopropanone equivalent.^{5,6}

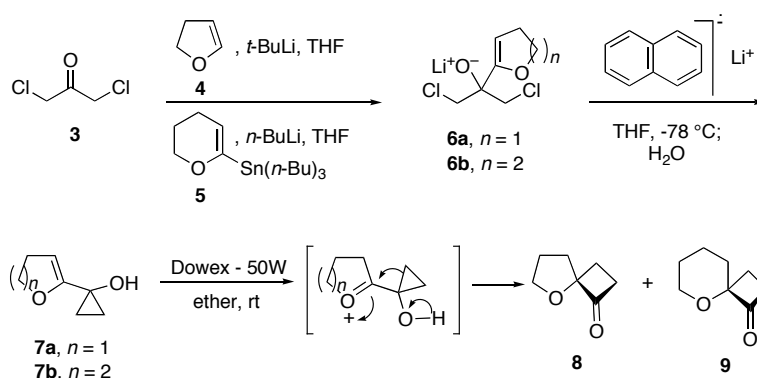


The useful expansion of this synthetic technology begins with the 1,2-addition of a lithiated vinyl ether to **3** as shown in Scheme 1. While the direct metalation of 2,3-dihydrofuran (**4**) proceeds well,⁷ recourse to

[‡]This paper is dedicated to the memory of Professor Kenji Koga, whose many innovative contributions to organic chemistry have contributed in significant ways to the development of the field.

the tin derivative (**5**) is a more efficacious protocol in the pyran series.⁸ Subsequent direct introduction of lithium naphthalenide in THF at $-78\text{ }^{\circ}\text{C}$ gives rise exclusively to the 1-substituted cyclopropanols (**7a**) and (**7b**), respectively. When ethereal solutions of these reactive carbinols are stirred overnight in the presence of Dowex-50W, oxonium ion-initiated pinacolic ring expansion^{2,9} operates to provide **8** and **9** in overall yields of 65% and 75%. Neither of these two hetero spiro cyclobutanones have been described previously.

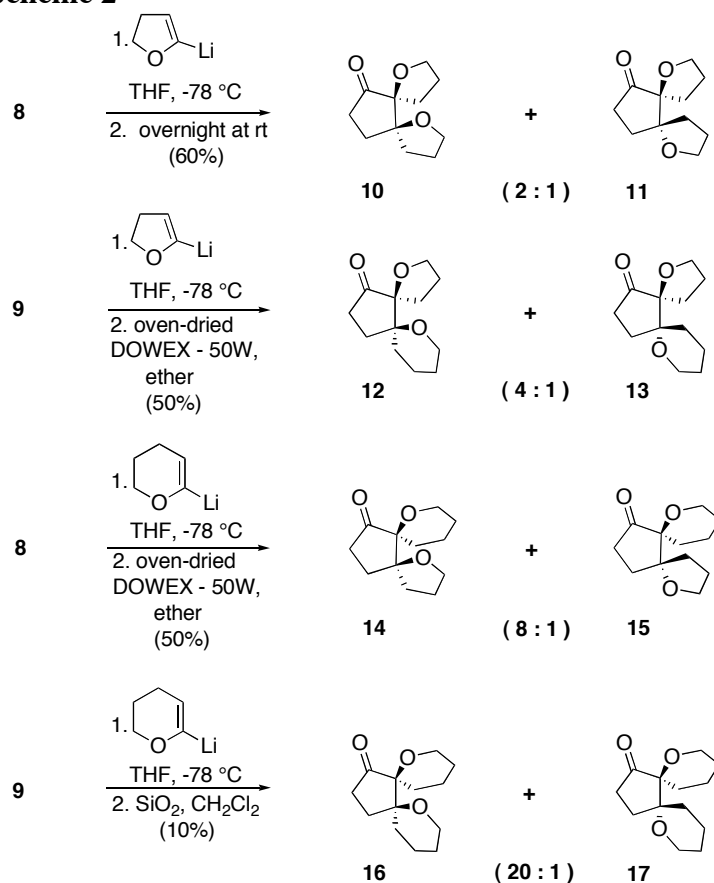
Scheme 1



When **8** was treated with lithiated dihydrofuran, smooth conversion to a mixture of two tertiary carbinols resulted. When attempts to induce their acid-catalyzed rearrangement was met with hydrolysis of the vinyl ether functionality, recourse was made instead to the overnight storage of neat samples at $20\text{ }^{\circ}\text{C}$. Presumably, traces of acid in a moisture-free environment induced the ring expansions. In these examples, the pinacol ring expansion is highly favored thermodynamically, such that a 2:1 mixture of **10** and **11** results. As in all related examples, the *syn* isomer is significantly more polar than its *anti* counterpart, thereby allowing the ready separation of **10** from **11** by silica gel chromatography (Scheme 2).

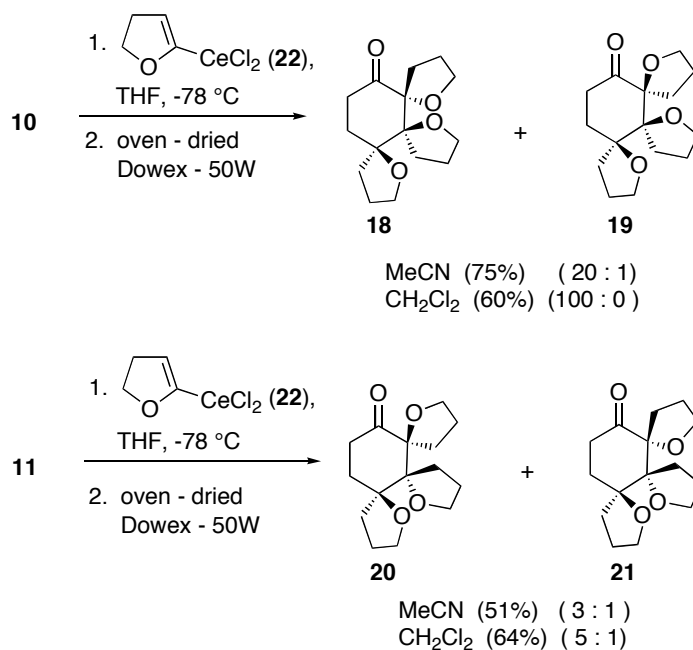
The reactivity pattern exhibited by **9** proved comparable, with the exception that simple acidic hydrolysis no longer competed with the pinacolic rearrangement. A slurry of Dowex-50W in dry ether delivered a 4:1 mixture of **12** and **13** in modest overall yield. Following the second-stage ring expansion of **8** with the lithiated dihydropyran (as generated from **5**) and subsequent exposure of the resulting carbinols to Dowex-50W resin, the cyclopentanones (**14**) and (**15**) were generated in a ratio rich in the *syn* isomer. In contrast, the pair of carbinols formed by 1,2-addition of lithiated dihydropyran to **9** proved to be significantly less prone to isomerization and in fact underwent decomposition in the presence of ion exchange resin. This heightened sensitivity prompted the alternate use of silica gel in CH_2Cl_2 at $20\text{ }^{\circ}\text{C}$ for the generation of **16** and **17**. This conversion proceeds slowly, requires three days to complete, and is the least efficient of the subset. Nonbonded steric compression on the periphery of the cyclopentanone ring in the diastereomeric products is the obvious root cause of the kinetic retardation.

Scheme 2



The stereochemical assignments to **10-17** are soundly based on the divergent polarity characteristics of isomeric pairs, distinctive ¹H NMR spectral features, and independent chemical conversions to trispiro ketones of known structure¹⁰ such as **18-21** (Scheme 3). The latter transformations rely on the fact that a vinyl cerate such as **22** undergoes 1,2-addition to **10** and **11** while curbing nonproductive enolization.^{11,12}

Scheme 3



In summary, the use of 1,3-dichloroacetone (**3**) as a synthetic equivalent for cyclopropanone offers an experimentally simple, highly diversifiable approach to the repetitive introduction of geminally situated spirocyclic ether units around the perimeter of five- and six-membered rings. The versatility provided by **3** and the few laboratory steps required to reach any given target constitute attractive aspects of this chemistry.

ACKNOWLEDGEMENTS

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