First examples of Friedel–Crafts alkylation using ketals as alkylating agents: an expeditious access to the benzene-fused 8-oxabicyclo[3.2.1]octane ring system

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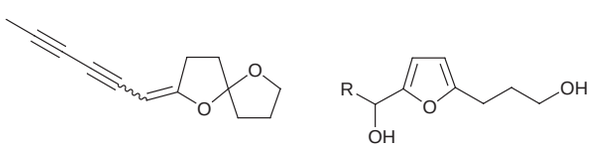
A novel acid-catalyzed intramolecular Friedel–Crafts alkylation (cyclization) using a spiroketal as electrophile leading to the otherwise not easily accessible benzene-fused 8-oxabicyclo[3.2.1]octane ring system in synthetically useful yields is reported. Slightly more than one equivalent of $BF_3{\cdot}OEt_2$ in THF at refluxing temperature are found to be the most satisfactory conditions to achieve the desired cyclization. An electron-donating group *para* to the position where cyclization will take place greatly facilitates the reaction.

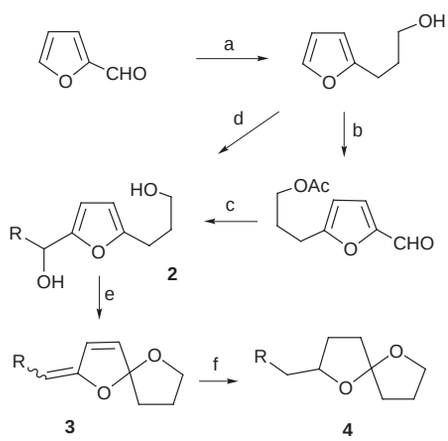
Friedel–Crafts alkylation[1] is a useful synthetic tool for construction of substituted aromatic compounds, both in the laboratory and in industry. The alkylating agents commonly used in this type of reactions include alkyl halides, alkenes, alcohols, ethers, epoxides, aldehydes and ketones. Recently, Fukuzawa[2] extended the scope of the alkylating agents to cover even acetals. They found that with trifluoromethanesulfonic acid or $Sc(OTf)_3$ as catalyst acetals reacted cleanly with arenes to give reductive alkylation products (the acetal carbonyl lost both oxygen links, becoming a CH_2). Using activated acetal–acetate as alkylating agent and $TiCl_4$ as catalyst, Rychnovsky[3] also realized intramolecular Friedel–Crafts alkylations in high yields. However, to the best of our knowledge cases of synthetic significance with ketals as alkylating agents have never been reported (although the efforts to widen the extent of the alkylating agent can be traced back many decades), presumably due to the low activity of the ketal functionality. Herein we wish to disclose an intramolecular version of such reactions, which not only extends the scope of the Fiedel–Crafts reaction but also provides an expeditious route to the interesting, yet not easily accessible benzene-fused 8-oxabicyclo[3.2.1]octane ring system.

In an earlier project[4] directed to the total synthesis of the insect antifeedant tonghaosu (**1**), a natural product isolated[5]



1 **2**

from *Chrysanthemum segetum L.* (*Compositae*) *etc.*, it was discovered in our laboratory that $CuSO_4$ could catalyze cyclization of some furan alcohols of the general formula **2**, where R is a substituent with a delocalized π-system (typically an aromatic ring or acetylenes). This facile cyclization was soon proved to be an efficient way to prepare spiroketals from easily available planar precursors (Scheme 1). Hydrogenation of the C–C double bonds in **3** led to saturated cyclic ketal **4**. During the course of exploring the chemistry of this type of compounds, we obtained an entirely unexpected product (in 78% yield) when we treated the piperonal-derived **4a** with conc. HCl in MeOH (60 °C for 12 h). Using 1–1.5 equiv. of $BF_3{\cdot}OEt_2$ as the acid and THF as solvent, the yield was further raised to 83%. The ^{1}H,



Scheme 1 *Reagents*: (a) (i) malonic acid, pyridine, (ii) H_2/Pd-C, (iii) $LiAlH_4$; (b) (i) Ac_2O, pyridine, DMAP, (ii) DMF, $POCl_3$; (c) (i) RLi, (ii) $KHCO_3$; (d) (i) ^{n}BuLi, TMEDA, (ii) RCHO; (e) $CuSO_4$; (f) H_2/Pd-C.

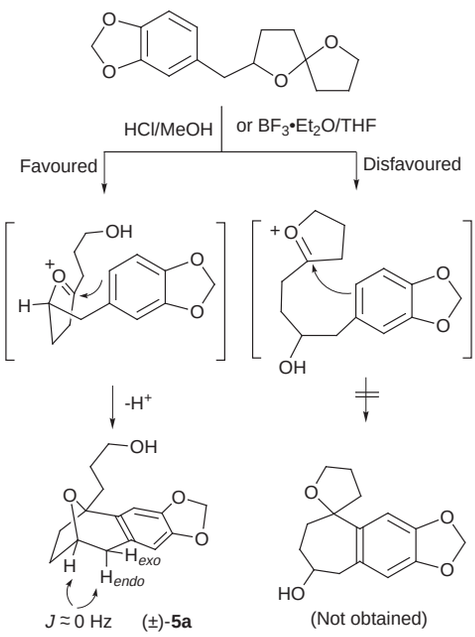
^{13}C NMR (including DEPT), IR, and MS spectra of this new compound and its acetate all point to the structure depicted for **5a**, where the benzylic protons at δ 2.39 (d, J = 16.2 Hz, 1H) and 3.15 (dd, J = 16.2, 5.1 Hz, 1H) have different dihedral angles (with respect to the bridgehead proton), explaining[6] why the two geminal protons show different splitting patterns in the ^{1}H NMR spectrum.

It appears that this unexpected cyclization most likely takes place *via* the mechanism shown in Scheme 2. The ketal carbonyl carbon is first activated by either protonation or coordination to a Lewis acid. Cleavage of the ketal O–C bond (a reversible process) in principle may occur at two sites. However, one of them would lead to formation of a seven-membered ring, which is normally difficult due to the conformational disadvantage, in the following step and therefore is strongly disfavored.

We also examined a few other sets of conditions (*e.g.*, TsOH or Amberlyst 15, toluene, reflux, 36 h), but none of them gave yields comparable to those mentioned above. Therefore in subsequent investigations reactions were carried out either with HCl, MeOH or $BF_3{\cdot}OEt_2$, THF (in the latter case addition of a small amount of MeOH remarkably accelerated the reaction). Trimethoxy derivative **4c** did not react so well, giving ~50% of the expected product **5c** (probably due to the increased steric congestion around the cyclization site). The *p*-methoxy-

Table 1 The results of intramolecular Friedel–Crafts alkylation (*cf.* Scheme 3)

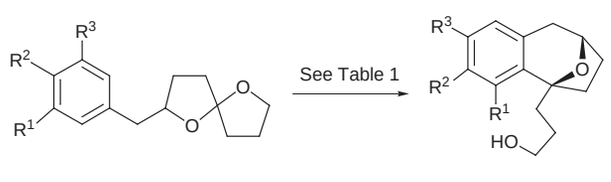
Spiroketal (**4**)	Product (**5**)	Method (yield %)
4a, R^1 = H, R^2–R^3 = –OCH_2O–	(±)-**5a**, R^1 = H, R^2–R^3 = –OCH_2O–	A (70), B (85)
4b, R^1 = R^3 = H, R^2 = OMe	(±)-**5b**, R^1 = R^3 = H, R^2 = OMe	(No reactions)
4c, R^1 = R^2 = R^3 = OMe	(±)-**5c**, R^1 = R^2 = R^3 = OMe	A (<30), B (47)
4d, R^1 = H, R^2 = OBn, R^3 = OMe	(±)-**5d**, R^1 = H, R^2 = OBn, R^3 = OMe	A (73), B (89)
4e, R^1 = R^2 = H, R^3 = OMe	(±)-**5e**, R^1 = R^2 = H, R^3 = OMe	A (60), B (73)
4f, R^1 = R^2 = H, R^3 = Me	(±)-**5f**, R^1 = R^2 = H, R^3 = Me	A (56), B (65)
4g, R^1 = R^2 = H, R^3 = *p*-tolyl	(±)-**5g**, R^1 = R^2 = H, R^3 = *p*-tolyl	A (70), B (78)



Scheme 2

substituted compound **4b** simply failed to react under the same conditions. However, with another dialkoxyl derivative **4d** as starting material, which has similar electron density on the aromatic ring and the same steric bulk at the cyclization position as in **4a**, the reaction gave the expected **5d** in 73% and 89% yields in the presence of HCl, MeOH or BF_3·OEt_2, THF, respectively.

The failure with **4b** may be interpreted in two different ways. One is that the overall electron density is not high enough as there is only one electron-donating methoxy group on the aromatic ring. The other is that the electron density at the cyclization site is not high enough, because it is *meta* to the methoxy substituent. In order to find out which is the case, *meta*-methoxy derivative **4e** was then prepared and subjected to the same reaction conditions. The outcome of the reaction was very gratifying. The expected **5e** was indeed formed in 60% (73%) isolated yield (Scheme 3 and Table 1). We next tested



Scheme 3

even weaker electron-donating groups such as the methyl and phenyl groups. Again, both **4f** and **4g** underwent the cyclization very smoothly to afford the corresponding bridge compounds **5f** and **5g** in good yields, but only under the BF_3·OEt_2, THF conditions.

It is interesting to note that the intramolecular hydride transfer[7] previously observed on several occasions with similar spiroketal opening processes somehow (perhaps due to the conformational deviation of the transferring hydride in the five-membered ring from the six-membered ring) does not occur (at least not to any significant extent) in the present system. As a consequence, one of the original ketal C–O bonds is retained in the product, forming an oxygen bridge. Cleavage of either bond at this bridge by various means may lead to a multifunctionalized seven-membered ring and thus open up opportunities for further synthetic endeavours.

Fused 8-oxabicyclo[3.2.1]octanes are of remarkable synthetic importance on their own. This was recently pointed out by Marson, who developed a novel approach[8] to such ring systems based on $SnCl_4$-catalysed intramolecular Friedel–Crafts alkylation with *e.g.*, hemistannyl acetals (formed *in situ* from epoxides) as alkylating agents. Through the demonstration of the feasibility of cyclization with spiroketals (which are sterically more hindered and therefore less reactive than acetals) as the electrophile, our protocol promises a unique opportunity to substitute the bridgehead proton with a functionalized carbon chain and provides a quick access to a subclass of bridged compounds with a tertiary carbon at the bridgehead. A variety of synthetic consequences may hence result.

Experimental

All chemicals and solvents (C.P. or A.R. grade) were used as received without any further purification.

General procedure for preparing spiroketal 4

Compound **3** (0.5 mmol)[4] was dissolved in EtOH (99.5%, 10 cm^3) containing a small amount of NEt_3 (0.05 mmol) and 10% Pd–C (10 mg). The mixture was then hydrogenated under atmospheric pressure until 2 equiv. of hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (eluting with 10 : 1 hexanes–EtOAc) to give pure **4** (~90% yields).

General procedure for intramolecular Friedel–Crafts alkylation

Method A. To a solution of the starting spiroketal **4** (1.0 mmol) in MeOH (10 cm^3) was added conc. HCl (0.13 cm^3, 1.5 mmol). The mixture was heated to reflux under N_2 for 12 h before being cooled to room temperature, diluted with diethyl ether (100 cm^3), washed with aq. sat. $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The crude product after removal of drying agent and solvents was subjected to column chromatography on silica gel (eluting with 2 : 1 hexanes–EtOAc) to give the pure product **5**.

Method B. The same as method A except that BF_3·OEt_2 (0.2 cm^3, 1.5 mmol) and THF (10 cm^3) plus 1–2 drops of MeOH were used in place of HCl and MeOH, respectively.

Spectroscopic data for 5a. δ_C(75 MHz, CD_3COCD_3) 146.62 (q), 146.41 (q), 136.48 (q), 126.57 (q), 109.73 (CH), 104.46 (CH), 101.30 (CH_2), 83.27 (q), 74.35 (CH), 62.49 (CH_2), 42.75 (CH_2), 37.74 (CH_2), 32.75 (CH_2), 30.25 (CH_2), 28.48 (CH_2); δ_H(300 MHz, CD_3COCD_3) 6.69 (s, 1H), 6.55 (s, 1H), 5.90 (s,

2H), 4.60 (m, 1H), 3.56 (m, 2H), 3.15 (dd, *J* 16.2, 5.1 Hz, 1H), 2.39 (d, *J* 16.2 Hz, 1H), 2.32–1.51 (m, 8H); *m*/*z* (%) 262 (M^+, 15.5), 233 (100), 215 (10.9), 203 (23.8), 190 (13.4), 175 (46.6), 145 (19.3); ν_{max}(film)/cm^{-1} 3410; HRMS: Calc. for $C_{15}H_{18}O_4$: 262.1205. Found: 262.1211.

Spectroscopic data for 5a acetate. δ_H(300 MHz, CD_3COCD_3) 6.58 (s, 1H), 6.53 (s, 1H), 5.88 (s, 2H), 4.67 (m, 1H), 4.10 (m, 2H), 3.24 (dd, *J* 16.1, 5.1 Hz, 1H), 2.36 (d, *J* 16.1 Hz, 1H), 2.30–1.60 (m, 8H); *m*/*z* (%) 304 (M^+, 78.4), 275 (100), 215 (42.5), 203 (43.5), 189 (11.7), 175 (54.3), 145 (18.5); ν_{max}(film)/cm^{-1} 1737.

Spectroscopic data for 5c. δ_H(300 MHz, $CDCl_3$) 6.37 (s, 1H), 4.70 (m, 1H), 3.85 (s, 6H), 3.80 (s, 3H), 3.59 (m, 2H), 3.30 (dd, *J* 16.2, 4.7 Hz, 1H), 2.60 (br s, 1H), 2.36 (d, *J* 16.2 Hz, 1H), 2.19–1.65 (m, 8H); *m*/*z* (%) 308 (M^+, 45), 279 (100), 263 (37), 249 (39), 221 (77); ν_{max}/cm^{-1} 3434; HRMS: Calc. for $C_{17}H_{24}O_5$: 308.1624. Found: 308.1615.

Spectroscopic data for 5d. δ_H(300 MHz, $CDCl_3$) 7.42–7.26 (m, 5H), 6.80 (s, 1H), 6.54 (s, 1H), 5.18 (d, *J* 12.7 Hz, 1H), 5.09 (d, *J* 12.7 Hz, 2H), 4.71 (m, 1H), 3.85 (s, 3H), 3.49 (m, 2H), 3.28 (dd, *J* 16.1, 4.7 Hz, 1H), 2.39 (d, *J* 16.1 Hz, 1H), 2.30–1.60 (m, 8H); *m*/*z* (%) 354 (M^+, 11), 325 (5.4), 263 (30.8), 149 (56.3), 91 (100); ν_{max} (film)/cm^{-1} 3400 (br); HRMS: Calc. for $C_{22}H_{26}O_4$: 354.1831. Found: 354.1855.

Spectroscopic data for 5e. δ_H(300 MHz, $CDCl_3$) 7.03 (d, *J* 8.5 Hz, 1H), 6.69 (dd, *J* 8.4, 2.7 Hz, 1H), 6.63 (s, 1H), 4.62 (m, 1H), 3.73 (s, 3H), 3.54 (m, 2H), 3.20 (dd, *J* 16.3, 6.4 Hz, 1H), 2.47 (d, *J* 16.3 Hz, 1H), 2.33–1.58 (m, 8H); *m*/*z* (%) 248 (M^+, 36), 231 (17), 219 (100), 189 (11), 161 (49); ν_{max}(film)/cm^{-1} 3402; HRMS: Calc. for $C_{15}H_{20}O_3$: 248.1413. Found: 248.1442.

Spectroscopic data for 5f. δ_H(300 MHz, $CDCl_3$) 6.97 (m, 2H), 6.90 (s, 1H), 4.74 (m, 1H), 3.61 (m, 2H), 3.32 (dd, *J* 16.3, 5.1 Hz, 1H), 2.44 (d, *J* 16.2 Hz, 1H), 2.28 (s, 3H), 2.49–1.71 (m, 8H); *m*/*z* (%) 232 (M^+, 26), 203 (100), 173 (23), 160 (21), 145 (75), 115 (18); ν_{max}(film)/cm^{-1} 3393; HRMS: Calc. for $C_{15}H_{20}O_2$: 232.1464. Found: 232.1470.

Spectroscopic data for 5g. δ_H(300 MHz, $CDCl_3$) 7.58–7.11 (m, 7H), 4.80 (m, 1H), 3.67 (m, 2H), 3.42 (dd, *J* 16.3, 4.9 Hz, 1H), 2.66 (d, *J* 16.3 Hz, 1H), 2.39 (s, 3H), 2.56–1.73 (m, 8H); *m*/*z* (%) 308 (M^+, 39), 290 (12), 279 (100), 249 (19), 221 (45), 97 (29); ν_{max}(film)/cm^{-1} 3410; HRMS: Calc. for $C_{21}H_{24}O_2$: 308.1776. Found: 308.1770.

Acknowledgements

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