Aliphatic C–H Activation with Aluminium Trichloride–Acetyl Chloride: Expanding the Scope of the Baddeley Reaction for the Functionalisation of Saturated Hydrocarbons

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The functionalisation of decalin by means of an “aliphatic Friedel–Crafts” reaction was reported over fifty years ago by Baddeley et al. This protocol is of current relevance in the context of C–H activation and here we demonstrate its applicability to a range of other saturated hydrocarbons. Structural elucidation of the products is described and a mechanistic rationale for their formation is presented. The “aliphatic Friedel–Crafts” procedure allows for production of novel oxygenated building blocks from abundant hydrocarbons and as such can be considered to add significant synthetic value in a single step.

Introduction

C–H activation is currently of great interest to the synthetic community. In contrast to conventional functional group interconversions, C–H activation represents an alternative paradigm whereby functionality may be introduced where none was present before. Such methodology enables the use of wholly new retrosynthetic approaches to complex molecule synthesis.

Applications of C–H activation in synthesis may be broadly subdivided into those reactions carried out on substrates with extensive existing functionality and those carried out on substrates that have minimal functionality or are entirely unfunctionalised. In the former category, desirable characteristics are chemo- and regioselectivity as well as functional group compatibility, which can restrict the reaction conditions that may be employed. These transformations often employ expensive transition metal catalysts for this “late stage” C–H activation, which can be considered to be justified in terms of the high value products that can be produced. In contrast, in the latter category, the absence of functionality potentially allows a wider range of reaction conditions to be used without unwanted side reactions. However, since the C–H functionalisation of a saturated hydrocarbon will almost certainly be the first step of a synthetic sequence, it is harder to justify the use of expensive transition metal catalysts. Rather, if the reaction is to be carried out on a significant scale, the cost of the reagents for C–H activation and also the cost of the substrate itself are key considerations if the transformation is to be synthetically useful.

In this latter context, reports from Baddeley on the reaction of decalin with aluminium trichloride and acetyl chloride are noteworthy. When an excess of aluminium trichloride is employed, the reaction furnishes multiple products (Scheme 1a). However, when an excess of acetyl chloride is employed at a lower temperature, tricyclic enol ether is formed cleanly (Scheme 1b).

Such “aliphatic Friedel–Crafts” acetylations have been reported for other unfunctionalised alkanes and alkenes; the products have been used in synthesis and the field has been reviewed. However, the decalin case is uniquely attractive from the standpoint of C–H functionalisation, since not only are the substrate and reagents inexpensive bulk commodity chemicals, but also the product is formed in reasonable yield and has a boiling point which is distinct from that of the starting material. The boiling points of any byproducts. This permits large-scale purification without recourse to chromatography; we have prepared pure by distillation on a 7 g scale. Functionalised decalins are key building blocks for terpenoid and steroid natural products and are also important in the fragrance industry; indeed, has seen diverse synthetic applications. Other examples of the functionalisation of decalin with aluminium trichloride include the use of benzenesulfonyl chloride to form several mono substituted chlorodecalins. We identified...
several saturated hydrocarbon substrates for which such aliphatic Friedel–Crafts reactions have not been reported and from which synthetically valuable products might be accessed. Products that were obtained from these substrates are described in this paper.

Results and Discussion

Mechanistic rationalisation of Baddeley’s transformation is important to aid in the structural elucidation of any products that form from its application to other substrates. Baddeley’s original proposal invoked an oxonium intermediate incorporated into a 4-membered ring (Scheme 2). Such an intermediate would be exceedingly strained; subsequently, Santelli et al. were the first to propose a variant on this mechanism which did not include such a strained oxonium. Our mechanistic proposal (Scheme 3) has several features in common with the previous proposals. In the absence of unsaturation for the acylating agent to react with, it instead acts as a hydride sink (such reactivity is precedent), leading to the formation of a tertiary cation at the decalin ring junction. Loss of a proton affords $\Delta^9,10$-octalin. A second equivalent of acylating agent reacts with the newly introduced unsaturation to give cation 13. Rather than formation of a 4-membered ring, we propose a [1,2]-hydride shift and attack of the oxygen at the position $\alpha$- to the ring junction, as in Santelli’s proposal. Such a process may be concerted or stepwise. Finally, on work up, loss of a proton affords enol ether 6. Overall, our proposal differs from Santelli’s in that 13 and 9 possess an sp$^2$ carbon (Santelli proposes this carbon to be sp$^3$ with a bond to a chlorine, cf. 10 and 11). In situ reaction monitoring by NMR spectroscopy shows formation of 9 prior to work up. Key proton $\Delta^9$ is observed at 6.08 ppm in the $\Delta^1$H-NMR spectrum, a comparable shift to similar compounds in the literature.

The proposal that the initial C–H activation step proceeds by hydride abstraction guided our choice of other hydrocarbon substrates for Baddeley’s protocol. Specifically, we selected only those able to form tertiary carbocations by hydride abstraction, i.e. those possessing (non-bridgehead) methines. In the first instance, we sought commercially available and inexpensive substrates. Bicyclohexyl meets these criteria, being produced by hydrogenation of the kerosene fraction of coal distillate. Thus, in the first instance, bicyclohexyl was subjected to the reaction conditions determined by Baddeley to be optimal for production of 6 from decalin. Gratifyingly, $\Delta^1$C-NMR analysis of the crude reaction mixture after workup indicated the presence of a single product in addition to unreacted bicyclohexyl (Scheme 4).

Structural elucidation of 15 was by means of DEPT and 2D NMR experiments in conjunction with crystallographic studies on derivatives (vide infra). The observations that both sp$^2$ carbons and one sp$^3$ carbon in 15 were quaternary and that a methyl group was present (3H singlet in the $\Delta^1$H spectrum) led to the proposal of the structure shown, on the basis of the mechanism given in Scheme 5. Abstraction of the tertiary hydride gives cation 16, from which two isomeric alkenes are accessible. In contrast to the decalin case (where the tetrasubstituted alkene is formed), we propose that loss of a proton from 16 leads to trisubstituted alkene 18 as opposed to 17. Regioselective reaction with a second acylium ion gives the second tertiary cation intermediate 19. Attack of the oxygen and [1,2]-hydride shift, analogous with the decalin case, forms the spiro-centre and gives oxonium 20. Of the two isomeric enol ethers available from deprotonation of 20, it is 15 that is formed in preference to 21. That neither cyclohexyl ring undergoes ring contraction is noteworthy, as AlCl$_3$-mediated formation of 2,2'-dimethylbicyclopentyl from cyclohexyl (in the absence of acetyl chloride) has been reported.

Scheme 2. Baddeley’s and Santelli’s mechanistic proposals.

Scheme 3. Our mechanistic proposal.

Scheme 5. C–H Activation of bicyclohexyl.

DFT modelling studies (M06/6-31G(d) basis set) support the contention that in the bicyclohexyl case, formation of trisubstituted alkene 18 is favoured over tetrasubstituted alkene 17. The transition state for formation of 18 via deprotonation of cation 16 by a chloride anion was calculated to be lower in energy by 10.8 kJ mol\(^{-1}\) than the corresponding transition state for formation of 17 (Figure 1a). Alkene 18 is also the thermodynamic product, lower in energy than 17 by 2.4 kJ mol\(^{-1}\). In contrast, the situation is reversed for decalin, wherein the transition state for formation of \(\Delta^{9,10}\)-octalin 7 from cation 12 was found to be lower in energy by 31.6 kJ mol\(^{-1}\) than the corresponding transition state for formation of its trisubstituted alkene isomer, \(\Delta^{1,9,10}\)-octalin (Figure 1b); \(\Delta^{9,10}\) -octalin 7 was also calculated to be lower in energy than \(\Delta^{1,9}\)-octalin by 6.7 kJ mol\(^{-1}\). This quantitation of \(\Delta \Delta G^\ddagger\) for the divergent elimination pathways from cations 12 and 16 supports the mechanistic proposals in schemes 3 and 5; only few experimental data on directly comparable eliminations have been reported previously.\(^{19,20}\)

Complete separation of 15 from unreacted bicyclohexyl 14 proved problematic – complete removal of bicyclohexyl (b.pt. 227 °C / 1 atm) under vacuum distillation required elevated temperatures which induced rearrangement of 15. The rearrangement product was identified as 22, with the relative configuration being assigned on the basis of Karplus analysis\(^{21}\) of the \(^3J_{HH}\) coupling constants for the ketone \(\alpha\)-methine (Scheme 6). The identity of 22 was further confirmed by formation of a 2,4-dinitrophenylhydrazone derivative 23 and its x-ray crystallographic analysis (Figure 2).
Separation of enol ether 15 from unreacted bicyclohexyl 14 was also attempted by chromatography. In the event, 15 proved hygroscopic, undergoing quantitative incorporation of adventitious moisture upon contact with silica to give hydrate 24 (Scheme 7). This hydrate was amenable to x-ray crystallographic analysis, which confirmed the relative stereochemistry as shown in Figure 3.

Encouraged by the ease and selectivity with which 15 may be transformed into functionalised products, we sought to examine the analogous reaction of other bicycloalkyls. Bicyclopentyl 25 was subjected to Baddeley’s conditions with the expectation of obtaining a product analogous to 15. In fact, 25 instead furnished the same product 6 originally observed by Baddeley (Scheme 8). In addition, both cis- and trans-decalin were recovered. We rationalise the formation of 6 by a skeletal rearrangement of bicyclopentyl cation 26 occurring to give decalin cation 12 prior to any loss of a proton (formation of 6 then proceeds as per the decalin case). The observed formation of decalin itself in the reaction of 25 is also suggestive of this sequence of events. It should also be noted that AlCl$_3$-mediated isomerisation of bicyclopentyl to decalin (in the absence of acetyl chloride) is in fact a known process.$^{23}$

**Figure 2.** Solid state structure of 23. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius. Only one of two molecules in the unit cell is shown for clarity.

**Scheme 7.** Hydration of 15 upon chromatography.

**Figure 3.** Solid state structure of 24. Ellipsoids are represented at 50% probability. H atoms are shown as spheres of arbitrary radius. Only one of two molecules in the unit cell is shown for clarity.

We next examined substrates that shared the bicyclo[m.n.0]alkane skeleton of decalin. Hydrindane, the ring contracted bicyclo[4.3.0]nonane analogue of decalin, has been reported$^{20}$ to undergo the Baddeley reaction, albeit less cleanly, furnishing ring contracted analogues of 6. Thus, we instead examined the reactivity of bicyclo[5.4.0]undecane 28. Upon exposure to Baddeley’s conditions, 28 gave a mixture of an acylated species 29 and various enol ether products, of which only 29 proved to be isolable in pure form. Unambiguous assignment of 29 required extensive characterisation by NMR spectroscopic means at high frequency, to minimise overlap of resonances. The structure was assigned as follows. The presence of a ketone as sole sp$^2$ carbon in the $^{13}$C spectrum and a clear 3H singlet ($\delta$ 2.02 ppm) in the $^1$H spectrum implied a structure analogous with 2 (i.e. a monoacylated species having only 3 double bond equivalents in total, confirmed by mass spectrometry). Secondly, the existence of a quaternary sp$^3$ carbon environment (present in the $^{13}$C spectrum but absent in the HSQC spectrum) implies the acyl group is located on a ring junction.

Thirdly, a characteristic 3H doublet ($\delta$ 0.82 ppm, J 6.3 Hz) in the $^1$H spectrum was indicative of the presence of a methyl group adjacent to a methine, which we ascribe to a (precedented) ring contraction of the seven-membered ring.$^{61}$ Establishing which ring position bears the methyl group was more complex. An H2BC spectrum was acquired,$^{25}$ in which both tertiary carbon environments (the carbons bearing H$^9$ and H$^9$, see Scheme 9) showed clear coupling to H$. As the H2BC experiment only shows 2-bond H-C correlations, this served to establish unambiguously which ring carbon bears the methyl group. The gross structure of 29 having been assigned, the final elucidation of relative stereochemistry was by means of a NOESY spectrum. Specifically, a clear through-space coupling between H$^9$ and H$^9$ was observed, indicating that they are 1,3-diaxially disposed and finally confirming the structure of 29.

**Scheme 8.** C–H Activation of 25 and its transformation into 6 by skeletal rearrangement.
We also examined the reactivity of bicyclo[5.3.0]decane 30, isomeric with decalin. As per our other C₁₀ substrate, 25, the sole product was once again Baddeley’s original enol ether 6 (Scheme 10).

Scheme 10. C–H Activation of 30 and its transformation into 6 by skeletal rearrangement.

For each of the substrates described above, all the methines are equivalent. In contrast, isopropylcyclohexane 31 (available from reduction of cumene or α-methylstyrene) has two inequivalent sites of possible hydride abstraction. Whilst this increases the number of possible products that may be formed from 31 under Baddeley conditions, we nevertheless undertook to explore its C–H activation chemistry as it is commercially available and inexpensive. Application of the standard conditions gave a reaction mixture in which a single product predominated. NMR spectroscopic data indicated both sp² carbons to be quaternary and as such 32 was assigned the structure shown, analogous with the product derived from reaction of bicyclohexyl²⁸ (Scheme 11).


This functionalisation of 31 in the cyclohexane 2-position is regiocomplimentary to the functionalisation of 31 with GaCl₃ which reportedly exhibits a preference for the 3- and 4-positions. Unreacted 31 could be removed by cold trap vacuum distillation at room temperature, but attempted distillation of 32 itself resulted in decomposition to an intractable mixture.

Conclusions

We have demonstrated the applicability of Baddeley’s “aliphatic Friedel–Crafts” procedure to a range of saturated hydrocarbon substrates. A variety of novel oxygenated structures have been produced, identified and, in the case of bicyclohexyl, have been further elaborated. A mechanistic explanation has been proposed that rationalises Baddeley’s original results and also the formation of the products described here. We anticipate that the products described here will serve as useful building blocks in a variety of synthetic contexts.

Experimental

General

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. Solvents were dried and degassed by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to petroleum ether, bp 40–60 °C. TLCs were performed using aluminium-backed plates precoated with Alugram®SIL G/UV and visualized by UV light (254 nm) and/or KMnO₄ followed by gentle warming. Flash column chromatography was carried out using Davisil LC 60Å silica gel (35–70 micron) purchased from Fisher Scientific. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer with absorbances quoted as v in cm⁻¹. NMR spectra were run in CDCl₃ (unless otherwise specified) on Bruker Avance 250, 300, 400 or 500 MHz instruments at 298 K. Mass spectra were recorded with a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik). Aluminium trichloride (98%, #206911), Acetyl chloride (98%, #11,418-9) and 1,2-dichloroethane (99.8%, anhydrous, #284505) were purchased from Sigma-Aldrich. Caution was taken when using large quantities of possibly carcinogenic chlorinated solvents; reaction workup, product isolation and purification was performed in a fume hood with appropriate personal protective equipment employed.

3’-Methyl-5’,6’,7’,7a’-tetrahydro-4’H-spiro(cyclohexane-1,1’-isobenzofuran) 15

AcCl (28.3 g, 0.361 mol, 2.4 eq.) was added over 15 min to a suspension of AlCl₃ (30.0 g, 0.223 mol, 1.5 eq.) in CH₂Cl₂CH₂Cl (70 mL) and stirred for 20 min. The resulting yellow solution was
then cooled to 0 °C. Over 20 min, bicyclohexyl (25.0 g, 0.150 mol, 1.0 eq.) was added, and the reaction mixture stirred for a further 3 h. The resulting orange solution was gradually added to a vigorously stirred slurry of ice-water (500 mL); a cherry-red colour was observed. The reaction mixture was transferred to a separating funnel and extracted with CH₂Cl₂. Organic extracts were combined and washed with ice-water (2 × 250 mL), dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure on a rotary evaporator to give crude product.

Bicyclohexyl (19.9 g, 80%) was recovered by fractional distillation (64-66 °C, 1.6-1.7 torr), and the orange residue identified as 3'-methyl-5',6',7',7'-tetrahydro-4'H-spiro[cyclohexane-1',1''-isobenzofuran] 15 and bicyclohexyl 14 was subjected to column chromatography (2.5:97.5 EtOAc:pet). (3'S*,3'a'R*,7'a'R*)-3'-Methylhexahydro-3'H-spiro[cyclohexane-1',1''-isobenzofuran]-3'-ol 24 was identified as a white crystalline solid. m.p. 46-47 °C; Rₜ 0.35 (2.5:97.5 EtOAc:petrol); δₜ (500 MHz, CD₃OD) 2.10 (1H, s, -OH), 1.98-1.88 (1H, m), 1.80-1.66 (3H, m), 1.63-1.57 (1H, m), 1.57-1.38 (8H, m) 1.35 (3H, s, CH₃), 1.31-1.19 (2H, m), 1.14-1.03 (1H, m) ppm; δC (500 MHz, CD₃OD) 105.9, 83.7, 45.8, 44.2, 38.8, 34.3, 29.1, 26.3, 25.2, 24.1, 24.0, 23.9, 23.9, 23.0 ppm; m/z 3389, 2928, 2850, 1444, 1404, 1374, 1197, 1171, 1160, 1151, 1092, 1074, 946, 890, 875 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₄H₃₀O₂Na⁺)²⁺ 247.1669; found 247.1691.

1-((2'R*,4a*S*,8a*R*)-2-Methyldecahydrodaphnaphthalene-4a-yl)ethanone 29

AcCl (11.6 g, 0.236 mol, 2.4 eq.) was added over 5 min to a suspension of AlCl₃ (19.7 g, 0.148 mol, 1.5 eq.) in CH₂Cl₂/CH₃Cl (60 mL) with stirring. The resulting pale yellow solution was cooled to 0 °C and bicyclo[5.4.0]undecane, 28 (15.0 g, 0.099 mol, 1.0 eq.) was added over 20 min. The reaction mixture was left to stir at 0 °C for 5 h. The deeper yellow solution was slowly poured into a stirred ice-water slurry, turning orange and back to yellow. The organic layer was extracted with CH₂Cl₂ (3 × 100 mL), washed with brine and dried over MgSO₄, then filtered. The filtrate was concentrated under reduced pressure. Crude product purified by vacuum distillation (2.1-2.3 Torr, 76-90 °C) gave a mixture of enol ethers and 1-((2'R*,4a*S*,8a*R*)-2-methyldecahydrodaphnaphthalene-4a-yl)ethanone 29 (9.55 g) as the major product. This was purified further by column chromatography (100% pentane to 1:99 EtOAc:pentane) to give 29 as a single isomer (Rₜ 0.22 in 1:99 EtOAc:pentane) as a colourless oil (4.46 g, 23%). δₜ (400 MHz) 2.02 (3H, s, COCH₃), 2.01-1.96 (2H, m), 1.91-1.80 (1H, m), 1.75-1.68 (1H, m), 1.59-1.49 (3H, m [including 1.54, 1.0 eq, q, J 11.9 Hz, H'']), 1.48-1.36 (1H, m, H''), 1.32-1.04 (7H, m [including 1.25-1.22, 1H, m, H'']), 0.84 (3H, d, J 6.3 Hz, CHCH₃), 0.81-0.70 (1H, m) ppm; δC (100 MHz) 213.3 (C=O), 53.0 (4° C=C=O), 46.0 (3° CH=CH₂), 37.9, 37.9, 37.8, 33.6 (CH₂CH₂), 32.0, 29.0, 26.9, 26.0 (COCH₃), 23.5, 22.4 (CH₂CH₃) ppm; vmax 2922, 2856, 1700, 1453, 1352, 1299, 1209, 1184, 1164, 1135, 1113, 940, 914 cm⁻¹; HRMS (ESI+) m/z calcd for (C₁₃H₂₁O₂Na²⁺)²⁺ 217.1563; found 217.1564.

1,1,3-Trimethyl-1,4,5,6,7a-hexahydroisobenzofuran 32

AcCl (300 g, 3.82 mol, 2.4 eq.) was added over 20 min to a suspension of AlCl₃ (319 g, 2.39 mol, 1.5 eq.) in CH₂Cl₂/CH₃Cl (500 mL) and stirred for 20 min. The resulting yellow solution was cooled to 0 °C. Over 90 min isopropylcyclohexane 31 (200 g, 1.59 mol, 1.0 eq.) was added, and the reaction mixture stirred for a further 3.5 h. The resulting orange solution was gradually added to a vigorously stirred slurry of ice-water (500 mL); a cherry-red colour was observed, then orange. The reaction
mixture was divided into 5 portions; each one in turn was transferred to a separating funnel and extracted with 1,2-dichloroethane (2 × 100 mL). Organic extracts were combined and washed with ice-water (2 × 100 mL), dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Distillation was performed at room temperature under reduced pressure – unreacted isopropylcyclohexane was collected in a cold trap, as a mixture with a byproduct identified as 1-chloroethylecylactate. The residue was shown by NMR to contain 1,1,3-trimethyl-1,4,5,6,7,8-hexahydroisobenzofuran 32 as the major product. δ (250 MHz) 2.33-0.69 (18H, m) ppm; δC (75 MHz) 141.6 (C(Me)-O, 4°), 108.2 (-C-O, 4°), 83.3 (C=C-C, 4°), 53.6, 29.6, 28.5, 25.7, 24.2, 22.9, 11.2 ppm; TOF-MS (ESI+) m/z caleced for (C₁₇H₁₈O₄H⁺) 167.1436; found 167.1440.

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Notes and references


Further experimental evidence for the mechanism for formation of 15 was established by subjecting 1-cyclohexylcyclohexene 18 to similar reaction conditions: 1-cyclohexylcyclohexene 18 was synthesised via the reaction of cyclohexylmagnesium bromide and cyclohexanone,

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followed by dehydration over P$_2$O$_5$. 18 was then subjected to the Baddeley reaction conditions (modified to use 1.0 eq. each of AcCl and AlCl$_3$) and gave a mixture of vinyl ether 15 and unsaturated ketone 22 in 55% yield.


Isopropylcyclohexane is available for £244/L from Tokyo Chemical Industries.

For a complete consideration of all possible enol ether products, see the supporting information. Compound 32 has been reported previously, but complete NMR spectroscopic data were not disclosed. See: C. M. Cimarusti, J. Wolinsky, J. Org. Chem., 1966, 31, 4118-4121.