Regioselective Rearrangement

Unknown Camphor: Regioselective Rearrangement under Acylation in a CF₃SO₃H/(CF₃CO)₂O System

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Abstract: The utility of camphor in the chemical sciences is vast and well documented, yet the creation of camphor-derived potentially useful bicyclo[2.2.1]heptane scaffolds still remains one of the great challenges of synthetic organic chemistry. Herein, we show that CF₃SO₃H/(CF₃CO)₂O-mediated acylation of camphor with benzoic acids is accompanied by a cascade of alkyl and hydride shifts and opens access to a new type of polyfunctional isoborneol. In case of salicylic acids, camphor feels the presence of the ortho-hydroxy group in the aryl moiety, the influence of which provokes cleavage of the bicycloheptane skeleton to lead to monocyclic carvenone.

Introduction

Camphor is a natural compound that exerts a significant influence on the development of synthetic and theoretical organic chemistry. Owing to its unique chemical properties, a wide range of synthetic methods for the regiospecific and stereospecific functionalization of the different carbon atoms of camphor and its derivatives, various bond-cleavage reactions, and rearrangements have been reported.[1] So, camphor has been proven to be an attractive starting material for the preparation of numerous natural and synthetic biologically active compounds,[1,2] as well as for the construction of chiral catalysts,[3] chiral auxiliaries,[4] NMR shift reagents, and others.[5]

The ability of camphor to undergo easy carbocationic transformations is one of its unique features.[1] As far back as 1902 the English chemists Armstrong and Lowry wrote: "No substance known to us suffers rearrangement of its parts and undergoes a complete change of type more readily than does camphor."[6] Its chemical modification is often accompanied by fascinating Wagner–Meerwein and Nametkin rearrangements, as well as by 2,6-hydride shifts, and leads to unpredictable products. Therefore, camphor and its derivatives, relative to other simple organic molecules, have considerable potential for the creation of new molecular scaffolds.[7] However, synthetically useful methods for the stereo- and regioselective modification of camphor on the basis of skeletal rearrangements are limited to C₉ and C₁₀ sulfonation,[8,9] C₉ bromination,[10] and transformation into 1-substituted camphenes under the action of phosphorus chlorides (e.g., PCl₃/PCl₅),[11] trichloroacetic anhydride or trifluoromethanesulfonic anhydride (Scheme 1).[12,13]

Scheme 1. Known methods for the chemical modification of camphor on the basis of rearrangements. DTBMP = 2,6-di-tert-butyl-4-methylpyridine.

The last of these methods, the stereoselective synthesis of 1-camphenyl triflate,[13] was discovered almost three decades ago. Evidently, to create new synthetic applications of camphor, the development of new methods for its regio- and stereoselective modification is undoubtedly interesting for synthetic organic chemistry.

In the present work, the unexpected transformation of camphor (1) under CF₃SO₃H/(CF₃CO)₂O-mediated acylation with benzoic acids is disclosed. Our recent synthesis of β-diketones by the selective α-acylation of alkyl aryl ketones with carboxylic acids in trifluoromethanesulfonic acid (TFOH)/trifluoroacetic anhydride (TFAA) was the motivation for this research.[14] TFAA, which was used as a medium and an activating agent, eagerly formed acyl trifluoroacetates from the carboxylic acids. The presence of TFOH promoted enolization and increased the acylating ability of the acyl trifluoroacetates.
Results and Discussion

Our aim was to synthesize camphor-derived β-diketones by using benzoic acids \( \text{2} \) (ArCOOH; Ar = Ph (a), 4-MeC\(_6\)H\(_4\) (b), 4-ClC\(_6\)H\(_4\) (c), 4-PhC\(_6\)H\(_4\) (d), 2-HOC\(_6\)H\(_4\) (e), 2-HO-5-BrC\(_6\)H\(_3\) (f), 4-HOC\(_6\)H\(_4\) (g)) as acylating agents by this method. Taking into consideration the ease with which bornyl cation rearrangements occur, we expected that the TfOH/TFAA-mediated acylation of enantiomerically pure camphor would occur with racemization; therefore, substantially cheaper racemic camphor was used.

Surprisingly, we found that acylation of camphor with benzoic acids \( \text{2a–d} \) was followed by rearrangement of the bicyclic skeleton to give \( \text{3a–d} \) as previously unknown functional derivatives of isoborneol, e.g., exo-4-(2-aryl-2-oxoethyl)-3-hydroxy-7,7-dimethyl-1-(trifluoroacetoxy)bicyclo[2.2.1]heptanes (Scheme 2).

Notably, under classic conditions of the Claisen condensation, the reaction of camphor with acyl halides and acid esters gives 1,3-diketones and is not accompanied by rearrangement.[15] Our reactions were performed with a camphor (1)/acid 2/TfOH/TFAA molar ratio of 1:2:1.5:8 in dichloromethane at room temperature for 48 h. One molecule of benzoic acid is involved in the reaction, and the utilization of a smaller excess (1.5 equiv.) of 2 did not reduce the yields of isoborneols 3. By using 1 equiv. of benzoic acids 2 and/or 0.5 equiv. of TfOH, under the conditions used to synthesize diketones from alkyl aryl ketones and carboxylic acids,[14] the yields of 3a–d were considerably reduced. In the absence of the carboxylic acids, camphor was returned from the reactions, practically without change. Hydrolysis of the obtained trifluoroacetates under very mild conditions gave dihydroxy ketones 4a–d in excellent yields.

The structures of bicyclo[2.2.1]heptanes 3 and 4, previously unknown, were determined by a combination of conventional 1D and 2D NMR spectroscopy experiments (\(^1\)H NMR and \(^13\)C NMR, DEPT90, 135COSY, HSQC, and HMBC) and elemental analyses, in addition to X-ray structure analysis data for 3a, 3b, 4b, and 4c.[16] To gain patterns for the assignment of the \(^1\)H and \(^13\)C signals in the NMR spectra of compounds 3 and 4, full assignment of the \(^1\)H and \(^13\)C signals for compound 3a as a representative example was accomplished (see the Supporting Information for the \(^1\)H and \(^13\)C NMR spectroscopy data).

The exo configuration of the secondary hydroxy group of 3-hydroxy-7,7-dimethyl-4-phenacyl-1-(trifluoroacetoxy)bicyclo[2.2.1]heptane (3a) was determined on the basis of the magnitudes of the vicinal \( ^3J_{\text{H2n,H3n}} \) and \( ^3J_{\text{H2x,H3n}} \) coupling constants and the long-range \( ^4J_{\text{H2x,H6x}} \) coupling constant. Generally, the magnitude of the \( ^3J_{\text{H2x,H3n}} \) coupling constant for protons with a cis configuration is much larger (7–12 Hz) than that for protons with a trans orientation (2–6 Hz), and the presence of the appreciable long-range \( ^4J_{\text{H2x,H6x}} \) coupling constant is specific for W-aranged protons.[17] The observed magnitudes of \( ^3J_{\text{H2n,H3n}} = 8.6 \text{ Hz}, ^3J_{\text{H2x,H3n}} = 4.0 \text{ Hz}, \) and \( ^4J_{\text{H2x,H6x}} = 4.1 \text{ Hz} \) allowed the exo configuration for the hydroxy group at C3 to be unambiguously ascribed and allowed assignment of the methylene protons at C2 (Figure 1).

Scheme 2. Acylation of camphor (1) with benzoic acids 2a–d.

Figure 2. Molecular structure of 3b.
bly, the spatial arrangement of the benzoyl moiety is different in the structures of these compounds. The torsion angles C4–C10–C11–O2 are equal to 3.67° for 3b and 75.52° for 4b. This difference is the result of an O3–H3···O2 intramolecular hydrogen bond in 4b.

![Figure 3. Molecular structure of 4b.](image)

The obtained structural data allowed a plausible mechanism for the TfOH/TFAA-mediated acylation of camphor with benzoic acids to be assumed (Scheme 3).

At the first stage, O-trifluoroacylation of a carbonyl group with acyl trifluoroacetate I generated in situ leads to 4-(trifluoroacetoxy)camphene II and probably proceeds through successive formation of carboxylics A, B, and C as a result of Wagner–Meerwein (W.–M.) and Nametkin rearrangements, with following deprotonation of C. Next, benzoylation of the methylene group of II with anhydride I gives intermediate D, which easily undergoes Wagner–Meerwein rearrangement to give cation E. Final treatment of the mixture with water yields isobornyl product 3. The interaction of cations of type E with nucleophiles usually affords isobornyl products such as 3 despite the thermodynamic preference for the formation of bornyl derivatives. Curiously, in this reaction we observed dual reactivity of anhydride I – trifluoroacylation of the carbonyl group of camphor (hard nucleophilic center) and benzoylation of the double bond of camphene II (soft nucleophilic center) – in full compliance with the hard–soft acid–base principle. The formation of the hydroxy (NOT trifluoroacetate or triflate) group at the C3 atom is another peculiarity of the acylation process. This can be explained by hydrolysis of the formed triflic acid esters of alcohols 3 upon treatment of the reaction mixture with water.

![Figure 4. Racemization of precursor carbocations E.](image)

Reaction of (+)-(R)-1 with benzoic acid (2a) yielded racemic isoborneol rac-3a. Therefore, trapping of the corresponding carbocation E with water follows a racemizing 6,2-hydride shift (Figure 4). This confirmed the ease of racemization of the bornyl cations under the TfOH/TFAA conditions for the acylation of camphor.

![Scheme 3. Plausible mechanism for the formation of isoborneols 3a-d in the acylation of camphor (1) with benzoic acids 2a-d.](image)
The proposed mechanism is speculative and requires proof. Interestingly, 4-hydroxybenzoic acid was polymerized under the same conditions as a result of self-acylation, and camphor was returned from the reaction without change.

Conclusions

In this study we found that the trifluoromethanesulfonic acid/trifluoroacetic anhydride mediated acylation of camphor with benzoic acids radically depends on the nature of the acid used. In whole, the reaction is accompanied by regioselective Wagner–Meerwein and Nametkin rearrangements and provides possibilities of its modification.

Experimental Section

General Procedure for the TFOH/TFAA-Mediated Acylation of Camphor: A solution of camphor (1 mmol), carboxylic acid (1.5–2 mmol), and TFAA (1.07 mL, 8 mmol), and TFOH (132 μL, 1.5 mmol) was stirred at room temp. for 15 min. Triflic acid (132 μL, 1.5 mmol) was then added, and the resulting solution was kept under the conditions indicated in Scheme 2 (TLC monitoring). Volatile components of the mixture were evaporated under reduced pressure, and after quenching with water, the residue was redissolved in CH2Cl2 (20 mL), washed with 5% NaHCO3 (2 × 5 mL) and water (2 × 5 mL), and dried with MgSO4. The solvent was removed in vacuo, and the crude mixture was purified by silica gel chromatography (column 20 × 1.5 cm, n-hexane/CH2Cl2).

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