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# HOF•$CH_3CN$, Made Directly from $F_2$ and Water, as an Ecologically Friendly Oxidizing Reagent

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*Abstract*: The complex HOF•$CH_3CN$, made directly from fluorine and aqueous acetonitrile, was used for oxidation of secondary alcohols and for Baeyer Villiger oxidation of ketones. By using $^{18}O$ labeled reagent it was found that the ketone oxidation proceeds through the original dioxirane mechanism which Baeyer and Villiger suggested a century ago for reactions with peracids but was later discounted.

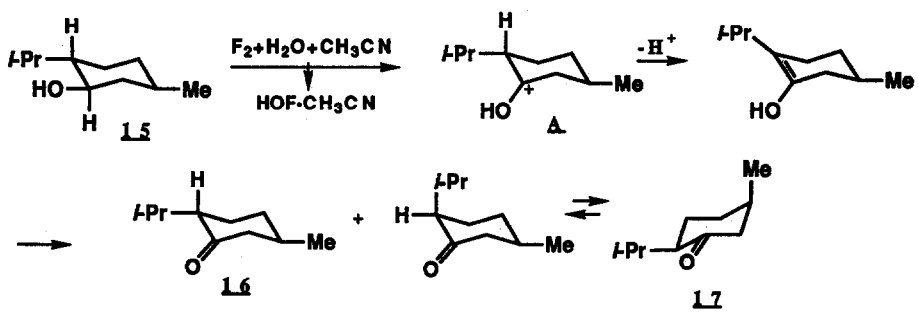
Professor Barton to whom this paper is dedicated, has contributed copiously to both fluorine chemistry[1] and our understanding of oxidation reactions, mainly through the unique "Gif systems".[2] We wish to combine here these two themes and describe a new powerful oxidative reagent based on fluorine which, unlike many other oxidants, does not contain any polluting heavy metals and is therefore ecologically friendly.

Passing elemental fluorine through ice results in formation of HOF.[3] Although this hypofluorous acid has been known for more than 20 years[4] it was practically unused in organic chemistry because of its extreme instability. A few years ago we developed a new way to prepare and stabilize it through complexation with acetonitrile. This opened new synthetic possibilities since the reagent possesses a strong electrophilic oxygen atom and as such is an excellent oxygen transfer agent. We have already used it to develop a novel direct epoxidation procedure good for most known double bonds,[5] to hydroxylate many tertiary unactivated CH bonds[6] and to oxidize aromatic[7] as well as aliphatic[8] amines to the corresponding nitro derivatives.

Oxidation of alcohols is, of course, as old as organic chemistry itself. Nevertheless, because it is essential to most fields of chemistry, new procedures are emerging continuously. Among these, phase transfer oxidations[9] and the use of dimethyldioxirane[10] are especially worth mentioning. We examine in this paper the scope of HOF•CH3CN towards oxidation of various alcohols in the absence, as well as in the presence, of other functional groups. This reagent is also capable of further oxidizing ketones to the corresponding esters in a reaction resembling the Baeyer Villiger rearrangement.

As an oxidizing agent, the HOF•$CH_3CN$ complex is unique in at least two categories. It possesses a permanent partially positive oxygen which speeds up the approach to the oxidizable center, while the eventual formation of the HF bond offers a very strong driving force for the process.[11] These combined features make HOF•$CH_3CN$ a very powerful oxidant indeed and 2-hydroxy-6-methylheptane (1) was oxidized already at 0 °C to 6-methyl-2-heptanone (2) in nearly quantitative yield (see table in the experimental section). Similar results were obtained with *cis*-1-hydroxydecalin (3) and 4-*t*-butylcyclohexanol (4) which were converted to *cis*-1-decalone (5) and 4-*t*-butylcyclohexanone (6) in less than 10 minutes. Although the reaction medium is acidic (for each molecule of HOF•$CH_3CN$ at least one molecule of HF is also formed) the low reaction temperature and the presence of water solvating the HF are responsible for the clean oxidation of acid sensitive compounds such as 3-pinanol (7) which is transformed in a very good yield to 3-pinanone (8). Another bicyclic derivative *l*-borneol (9) was similarly oxidized to *l*-camphor (10) indicating that chiral centers are generally not affected. This is also evident from the reactions with various steroids. Thus cholestanol (11) was transformed to cholestanone (12) and even the much less reactive hydroxyl at 17 in androstan-3-on-17-ol (13) was oxidized, forming androstan-3,17-dione (14) at 0 °C in 40 minutes. When menthol (15) was oxidized, a mixture of menthone (16) and the thermodynamically less stable isomenthone (17) was formed in a 4:1 ratio. Isomenthol (18) on the other hand, produced only 17.

*Scheme 1*

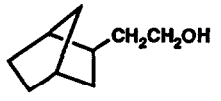



These results can be explained (Scheme 1) if we assume that the first step of the reaction is an attack on the hydride-like $\alpha$ hydrogen by the electrophilic oxygen atom of the HOF. An

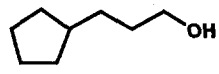
example for such an oxidation mechanism proceeding via hydrogen abstraction can be found in the oxidation of steroid ethers to ketones by $F_2$.[12] In the case of menthol the empty orbital of the carbocation **A** overlaps with the axial tertiary hydrogen at 2 leading to a some degree of enolization with a subsequent isomerization.[13]

An additional support for the initial oxidation step is provided by cyclohexanols substituted at the 2 position. The moderate steric hindrance of the methyl group in 2-methylcyclohexanol (**19**) is fully compensated by its positive inductive effect which increases the electron density of the $\alpha$ C-H bond so there is quantitative production of 2-methylcyclohexanone (**20**) in 10 minutes at 0 °C. An electron withdrawing group at this position on the other hand, lowers the electron density of this C-H bond considerably. As a result, the oxidation of 2-nitrocyclohexanol (**21**) to 2-nitrocyclohexanone (**22**) is very slow indeed and when an 1:1 molar mixture of **19** and **21** was reacted with 2 fold excess of HOF•CH3CN only **19** was oxidized and no traces of **22** were found. Working with 2-*t*-butylcyclohexanol (**23**), slowed the reaction considerably, but the electron donating ability of the *t*-butyl group overcame its bulkiness which obstructed the reaction center completing eventually the oxidation to 2-*t*-butylcyclohexanone (**24**). Such electronic effects are very important in electrophilic substitutions on saturated centers as already demonstrated in somewhat similar reactions with $F_2$.[14] Formation of ketals, or an attack on the oxygen atom of the alcohol forming a peroxy moiety with subsequent scrambling of the two oxygens, can be ruled out since the oxidation of **4**, for example, with $H^{18}OF•CH_3CN$[15] leads only to $^{18}O$ free **6**.

The electron density on hydrogens $\alpha$ to the hydroxyl group in primary alcohols is lower than in secondary ones. This is well reflected in the reactions of these alcohols with the reagent. With the exception of benzyl alcohol, which forms benzaldehyde in 60% yield, other primary alcohols such as **25** - **28** require very long reaction times and even then only 30 to 40% are converted to form mixtures containing aldehydes and acids. This difference in reactivity between primary and secondary alcohols, offers a good selectivity and diols such as 1,2- or 1,4-pentandiol (**29** and **30**) were easily partially oxidized to **31** and **32**[16] correspondingly.




**25**

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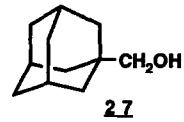


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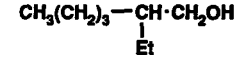


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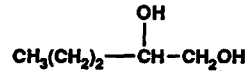
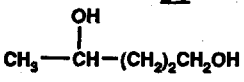
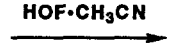
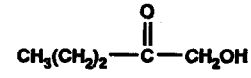



**29**

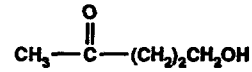



**30**



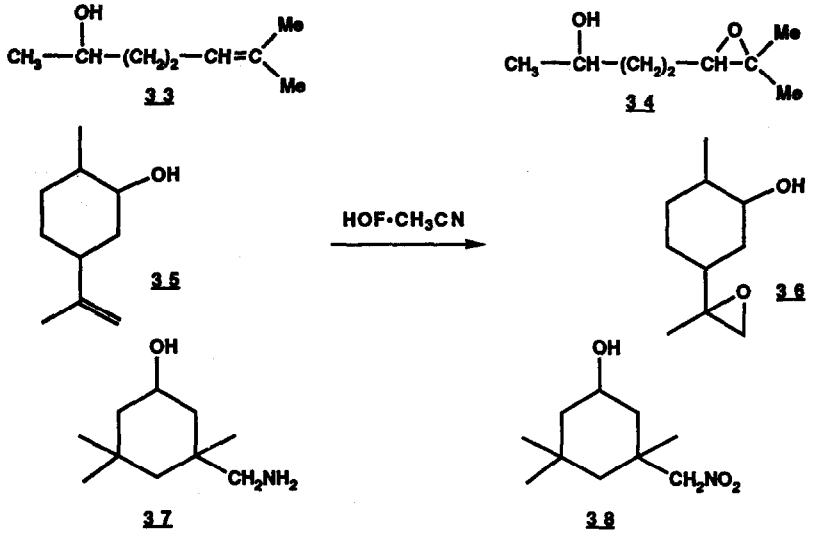




**31**




**32**

In order to evaluate the scope of this reaction several other types of alcohols had to be tested. Tertiary alcohols such as 3,6-dimethyl-3-heptanol are resistant to oxidation as might be expected, but secondary ones with additional functional groups posed more interesting challenges. Enols, for example, showed excellent selectivity and the olefinic center reacted much faster than the CHOH moiety. Thus 6-methyl-5-hepten-2-ol (33) reacted with the electrophilic HOF to form the corresponding epoxide (34) (Table 1). Even the less nucleophilic terminal olefin of dihydrocarveol (35) was exclusively epoxidized to 36 without any signs of simultaneous oxidation of the hydroxyl.[17] Another potential site for electrophilic attack is the amino group which also reacted faster than the alcohol moiety as evident from the reaction of 3-aminomethyl-3,5,5-trimethylcyclohexanol (37) converted to the corresponding nitro derivative (38) without affecting the alcohol group. Since olefins and amines are more electron rich centers than hydrogens $\alpha$ to hydroxyl, the above results are in accordance with the notion that the initial step of the alcohol oxidation by the hypofluorous acid is indeed an extraction of such hydrogens.

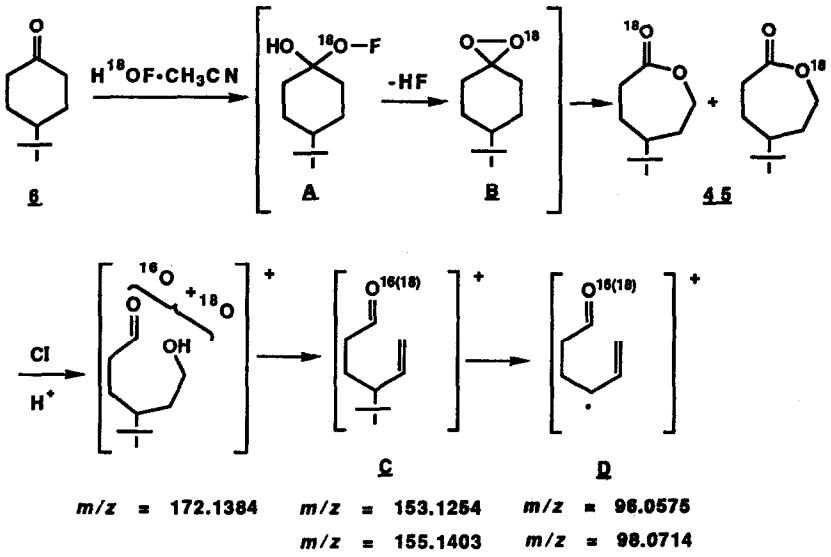



Ketones are much less reactive than the alcohols and one can oxidize the hydroxyl in the presence of a carbonyl as was already demonstrated in the case of androstan-3-one-17-ol (13). This, however, does not mean that ketones are totally unreactive. When treated with excess of HOF•$CH_3CN$ for longer periods they are further oxidized to the corresponding esters in a reaction similar to the Baeyer Villiger oxidation. Thus 2-methylcyclohexanone (20) and 1-decalone (5) were oxidized to the corresponding lactones 39[18] and 40. Straight chain ketones such as 2- or 5-nonanone (41) and (42) were also successfully converted to heptyl acetate (43)[19] and butyl butyrate (44)[20] in good yields.

Although the final products are the same as in the Baeyer-Villiger oxidation with peracids, one major difference is immediately notable. While the classical reaction with peracids usually requires high temperatures and many hours, with HOF•$CH_3CN$ the rearrangement is completed in 3 to 4 hours at 0 °C. This may well reflect a difference in the reaction mechanisms between the two reagents.

By using ketones labeled with the $^{18}O$ isotope, Doering in a classical study proved that the oxygen in the original ketone is also the carbonyl oxygen in the resulting ester and the etheric oxygen atom originates therefore from the peracid.[21] Ironically, this ruled out the original mechanism suggested by Baeyer and Villiger themselves,[22] since the dioxirane formation which they postulated as an intermediate leads to scrambling of the two oxygen atoms. We used the fact that it is very easy to introduce the $^{18}O$ isotope into the $H^{18}OF•CH_3CN$ reagent[15] and so reacted it with 4-t-butylcyclohexanone (**6**). After 4 hours at 0 °C we obtained the $^{18}O$ containing lactone **45**[23] in greater than 90% yield. Its CI mass spectrum (Scheme 2) showed a molecular peak *m/z* = 172.1384 indicating that only one of the oxygens was the $^{18}O$ isotope (calcd. for $C_{10}H_{18}{}^{16}O^{18}O$ : 172.1350). One characteristic fragment for the all $^{16}O$ **45** is *m/z* = 153.1254 $[(M + 1) - H_2O]^+$ (calcd. for $C_{10}H_{17}O$ : 153.1279) which originates from the cleavage of the CO-O bond with consequent protonation of the ether oxygen by the chemical ionization process followed by dehydration. Another dominant allylic fragmentation results in fragment **D**, *m/z* = 96.0588 (calcd. for $C_6H_8O$ : 96.0575). In our case, the mono $^{18}O$ labeled **45** showed two fragments of equal intensity of type **C**: *m/z* = 155.1403 (calcd. for $C_{10}H_{17}{}^{18}O$ : 155.1322) and 153.1254 (calcd. for $C_{10}H_{17}{}^{16}O$ : 153.1279). The fragment of type **D** also showed two peaks of equal intensity *m/z* = 98.0714 (calcd. for $C_6H_8{}^{18}O$ : 98.0618) and *m/z* = 96.0588 (calcd. for $C_6H_8{}^{16}O$ : 96.0575).

***Scheme 2***



The above fragmentation pattern clearly shows that the $^{18}O$ isotope is equally distributed among the two ester oxygen atoms. As with olefins, the initial attack of HOF•$CH_3CN$ is on the $\pi$ electrons of the carbonyl to form eventually intermediate **A**. The very favorable HF elimination is a strong driving force for the subsequent formation of the dioxirane moiety (intermediate **B**) which is responsible for a faster reaction compared to the peracids and for the scrambling of the two oxygen atoms in the resulting ester. We feel that this is a completion of a full cycle for the mechanism proposed by Baeyer and Villiger, discounted after 50 years by Doering, and coming back to life after a whole century, although with a different type of oxidant than the ones originally used.

## EXPERIMENTAL

$^1H$ NMR spectra were recorded with Bruker AC-200 with $CDCl_3$ as solvent and $Me_4Si$ as an internal standard. The proton broad band decoupled $^{13}C$ NMR spectra were recorded at 90.5 MHz. Here too, $CDCl_3$ served as a solvent and TMS as internal standard. High resolution mass spectra were measured with a VG micromass 7070H instrument. IR spectra were recorded as neat films, in $CHCl_3$ solution or in KBr pellets on a Nicolet 205 FTIR spectrophotometer.

### *General Procedure for Working with Fluorine*

Fluorine is a strong oxidant and a very corrosive material. An appropriate vacuum line made from copper or monel in a well ventilated area should be constructed for working with this element.[24] For the occasional user however, various premixed mixtures of $F_2$ in inert gases are commercially available, simplifying the whole process. The reactions themselves can be carried out in glass vessels. If elementary precautions are taken, work with fluorine is relatively simple and we have had no bad experiences working with this element.

### *General Procedure for Producing the Oxidizing Agent HOF•$CH_3CN$*

Mixtures of 10% $F_2$ with nitrogen were used in this work. The gas mixture was prepared in a secondary container before the reaction was started. This mixture was then passed at a rate of about 400 mL per minute through a cold (-10 °C) and vigorously stirred mixture of 400 mL $CH_3CN$ and 40 mL $H_2O$. The development of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. It is thus possible to achieve concentrations of more then a mol/liter of the oxidizing reagent.

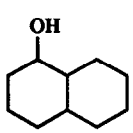
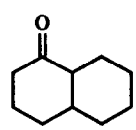
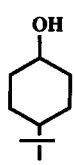
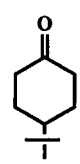
### *General Oxidation Procedure*

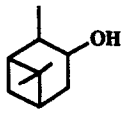
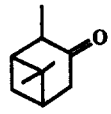
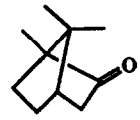
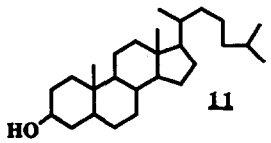
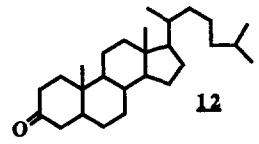
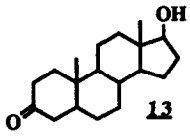
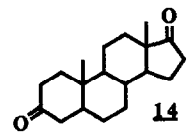
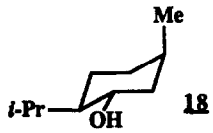
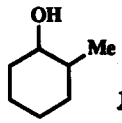
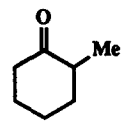
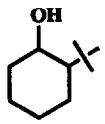
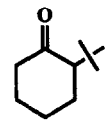
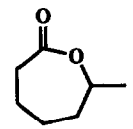
About 10 mmol of a secondary alcohol (or ketone) were dissolved in 10 - 20 mL $CHCl_3$. The mixture was then cooled to 0 °C and added to the reactor containing the cold (-10 °C to 0 °C) oxidizing HOF•$CH_3CN$. This was the temperature for all reactions since the reagent decomposes

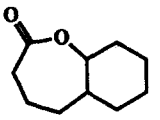
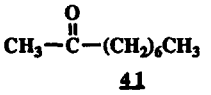
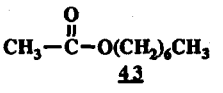
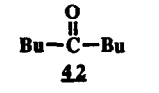
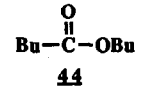
quite rapidly at higher temperatures. The reaction was monitored and stopped when a conversion of 85 - 95% was reached, since in some cases the Baeyer Villiger oxidation starts to take place relatively fast. Usually a 2 to 3 fold excess of the reagent for 5 to 40 minutes is needed but we were not able to quantify this factor since its decomposition rate may vary somewhat from one reaction to another. We have some indications that the more tertiary hydrogens a substrate contains, a larger excess of the reagent is needed, probably because of its affinity for such centers.[6] In any event, one should monitor the presence of the oxidative reagent in the reaction mixture iodometrically. In the case of primary alcohols usually more than 10 fold excess of HOF•$CH_3CN$ was used in order to reach conversion of 30 to 40 %. Even then we got mixtures of aldehydes, acids and other unidentified compounds which were not isolated. In the case of enols and amino-alcohols we used only one mole equivalent of the reagent in order to find out which functional group would react preferably. As for the Baeyer Villiger oxidation, 4 to 5 mole/equiv of the reagent were used and the reaction took 3 to 4 hours. After completion, the reaction was neutralized with saturated sodium bicarbonate solution, poured into water, extracted with $CHCl_3$ and washed with $NaHCO_3$ and water until neutral. The organic layer was dried over $MgSO_4$, and the solvent removed. The crude product was usually purified by vacuum flash chromatography using silica gel 60-H (Merck). The spectral and physical properties of the known products thus obtained were compared either with those of authentic samples or with the properties reported in the literature. In every case excellent agreement was obtained. Yields and specific reaction conditions for all compounds and more detailed data for new compounds or for ones which have not been well defined in the literature are given in the following table.

Table 1

$R_2CHOH + HOF•CH_3CN \rightarrow R_2CO;\ RCOR' + HOF•CH_3CN \rightarrow RCOOR'$

| Starting Material | Product | Reaction Time | Yield (%) |
|---|---|---|---|
| $Me_2CH(CH_2)_3-CHMe$ (OH) 1 | $Me_2CH(CH_2)_3-C(=O)-Me$ 2 | 30 min | 95 |
|  3 |  5 | 5 min | 95 |
|  4 |  6 | 2 min | 80 |

| | | | |
|---|---|---|---|
|  7 |  8[a] | 30 min | 90[25] |
|  9 |  10 | 30 min | 95 |
|  11 |  12 | 15 min | 80[b] |
|  13 |  14 | 40 min | 80 |
| 15 | 16 + 17 (4:1 ratio) | 60 min | 85[b] |
|  18 | 17 | 60 min | 90[b] |
|  cis/trans 19 |  20 | 10 min | 95 |
|  cis/trans 23 |  24 | 3.5 hrs | 90 |
| 33 | 34[c] | 2 min | 70 |
| 35 | 36[d] | 2 min | 90 |
| 37[e] | 38[f] | 10 min | 60 |
| 20 |  39 | 4 hours | 85[18] |

| | | | |
|---|---|---|---|
|  **5e** |  **40**[g] | 4 hours | 55 |
|  **41** |  **43** | 4 hours | 80[19] |
|  **42** |  **44** | 4 hours | 60[20] |
| **6** | **45** | 3 hours | 95[23] |

Notes for the Table: *a*) IR: 1712 $cm^{-1}$; $^1H$ NMR: 2.7-1.7 (7H, m), 1.32 (3H, s), 1.21 (3H, d, J = 8 Hz), 0.88 (3H, s); MS: *m/z*: 152 ($M^+$). *b*) These reactions required up to 8 fold excess of the oxidizer. *c*) Oil; IR: 3630, 1089 $cm^{-1}$; $^1H$ NMR: 3.65 (1H, m), 3.38 (1H, m), 2.33 (1H, s), 1.8-1.4 (4H, m), 1.27 (3H, s), 1.17 (3H, s), 1.12 (3H, d, J = 6 Hz); MS: *m/z*: 144 ($M^+$); Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.43; H, 11.42. *d*) Oil; IR: 3650, 1059, 1065 $cm^{-1}$; $^1H$ NMR: 3.1 (1H, dt, $J_1$ = 9 Hz, $J_2$ = 4 Hz), 2.87 (1H, bs), 2.66 and 2.53 (2H, AB system, J = 4.8 Hz), 2.1-1.5 (8H, m); 1.25 (3H, s), 1.00 (3H, d, J = 6.3 Hz); $^{13}C$ NMR: 59.14, 59.03 (quaternary C, for the 2 diastereomers), 53.17, 53.09 ($CH_2O$); MS: *m/z*: 152 [(M-$H_2O$)]$^+$; Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.29; H, 10.60. *e*) cis and trans mixture. *f*) mp 81 °C; IR: 3500, 1541, 1376 $cm^{-1}$; $^1H$ NMR: 4.62 and 4.28 (2H, AB system, J = 10.6 Hz), 4.21 (1H, s); 3.95 (1H, m); $^{13}C$ NMR: 88.92, 83.48 ($CH_2NO_2$, for the cis and trans isomers); MS: *m/z*: 186 [(M-Me)]$^+$; Anal. Calcd. for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.95; H, 9.45; N, 6.78. *g*) this compound was only isolated in 85% purity; IR: 1720 $cm^{-1}$; $^{13}C$ NMR: 81.78, 76.91 (*tert* CH-O), 41.43, 39.52 (*tert C*) the two pairs of signals are for the cis and trans isomers); MS: *m/z*: 168 ($M^+$).

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