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SHORT COMMUNICATIONS

On the Prins reaction of terminal olefins and formaldehyde in trifluoroacetic acid

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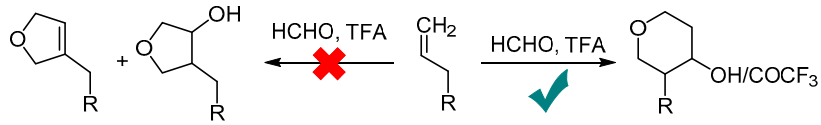
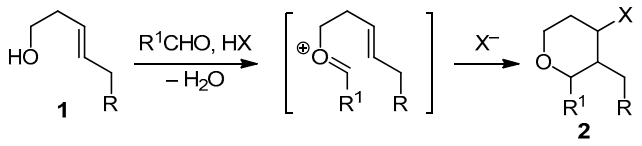


The Prins reaction of 1-heptene, as a representative terminal alkene, with formaldehyde in trifluoroacetic acid produces 3-butyl-4-(trifluoroacetoxy)tetrahydropyran and/or 3-butyl-4-hydroxytetrahydropyran; it does not provide (as previously reported by Talipov and coworkers) a route to 3-alkyl-2,5-dihydrofurans and 4-alkyl-3-hydroxytetrahydrofurans.

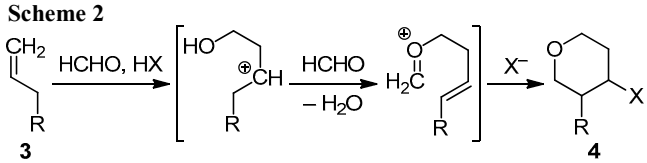
Keywords: formaldehyde, terminal alkenes, tetrahydropyrans, trifluoroacetic acid, Prins reaction.

Acid-induced reaction between homoallylic alcohols **1** and aldehydes (Prins cyclization) provides a straightforward entry to substituted tetrahydropyrans **2** (Scheme 1).[1] The original Prins reaction, using simpler terminal olefins **3**, can produce a range of products depending on the substrate and experimental conditions.[2] In general, the latter is not viewed as a useful strategy to tetrahydropyrans, although 3-alkyl-4-chlorotetrahydropyrans **4** (X = Cl) are accessible in good yields from terminal olefins using paraformaldehyde and gaseous HCl at low temperature (Scheme 2).[3] Using H_2SO_4 with formaldehyde and acetic acid or under aqueous conditions is known to generate 4-acetoxy- or 4-hydroxy-3-substituted tetrahydropyrans, together with significant quantities of 4-substituted 1,3-dioxanes.[4]

Scheme 1

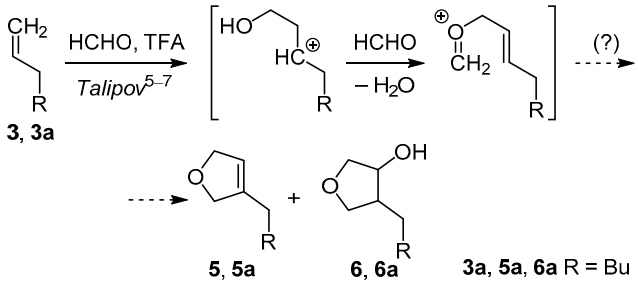


Scheme 2



Starting with 1993, Talipov and coworkers claimed in a series of papers,[5] a patent,[6] and a review article[7] that on switching to trifluoroacetic acid (TFA) as solvent the reaction of terminal olefins **3** and paraformaldehyde led, remarkably, to a mixture of 3-alkyl-2,5-dihydrofurans **5** and 4-alkyl-3-hydroxytetrahydrofurans **6** (4:1 to 2:1, depending on water content) in good overall yields (Scheme 3). Further studies (including kinetic and computational) on this latter transformation were subsequently reported, even up to 2015.[8] This process was also reported as being successful for higher aldehydes (using R^1CHO instead of HCHO) giving 2,3,5-trisubstituted 2,5-dihydrofurans,[5b] and (in this Journal) as giving a mixture of 4-alkyl-3-trifluoroacetoxy- and 4-alkyl-3-chlorotetrahydrofurans with formaldehyde and Me_3SiCl in TFA.[9] Herein, we disclose our reexamination of the reaction of a terminal alkene with formaldehyde in TFA.

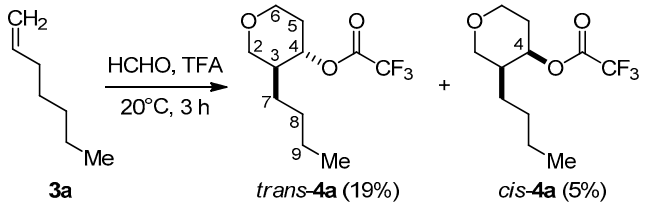
Scheme 3



The reaction of formaldehyde and 1-heptene (**3a**) (Scheme 3) in TFA was reported to give 3-pentyl-2,5-dihydrofuran (**5a**) in good yields and has been the most extensively investigated;[5a,b] consequently, this synthesis was reexamined. Following an exact experimental proce-

dure of Talipov, which reportedly gave a 43% yield of 3-pentyl-2,5-dihydrofuran (**5a**),[5b] 1-heptene (**3a**) was reacted with HCHO in TFA for 3 h at 20°C (a similar result was observed at 60°C). The major component we isolated was a nonpolar colorless oil, possessing ^{1}H NMR data (e.g., (400 MHz, $CDCl_3$), δ, ppm: 4.87 (1H, td)) similar to those reported by Talipov ((80 MHz, $CDCl_3$), δ, ppm: 4.63–5.09 (1H, m)).[5a,b] However, the data is inconsistent with that for 3-pentyl-2,5-dihydrofuran (**5a**) (e.g., (60 MHz, CCl_4), δ, ppm: 5.4 (1H, =CH)).[10a] Besides, 3-pentyl-2,5-dihydrofuran, prepared by us,[10b] displayed an olefinic proton ((400 MHz, $CDCl_3$), δ, ppm: 5.43–5.48 (1H, m, C=CH)) consistent with the earlier report.[10a]

Scheme 4



The material isolated under the Prins conditions in anhydrous TFA is most straightforwardly assigned as tetrahydropyranyl trifluoroacetates *trans*-**4a** and *cis*-**4a** (Scheme 4), which would arise from a reaction akin to that in Scheme 2 ($X^- = F_3CCO_2^-$). Indeed, our spectroscopic data is consistent with trifluoroacetate data reported by Talipov from the reaction mentioned above of terminal alkenes with formaldehyde and Me_3SiCl in TFA,[9] albeit Talipov assigned the products as 4-alkyl-3-trifluoroacetoxy-tetrahydro*furans*. Our 2D NMR data (^{1}H–^{1}H COSY, DEPT–HSQC, and ^{1}H–^{13}C HMBC, see Supplementary information file for spectra) provides strong evidence for 3,4-disubstituted tetrahydropyran structure **4a**. For structure *trans*-**4a**, ^{1}H–^{1}H COSY correlations between protons H-4 and H-3 and H_a-5/H_b-5 revealed the existence of a C-3/C-4/C-5 atom sequence, and the alkyl group is located at position C-3 based on DEPT–HSQC. ^{1}H–^{1}H COSY and DEPT–HSQC data showed that the protons at 3.19 ppm (1H, dd) and one H of the unresolved signal at 3.93–4.01 ppm (2H, m) belong to the C-2 methylene group, whereas the protons at 3.50 ppm (1H, ddd) and the second H of the signal at 3.93–4.01 ppm (2H, m) can be assigned to the C-6 methylene group. Both atom pairs H-2/C-6 and H-6/C-2 are connected by an ether linkage based on the HMBC spectrum, and long-range HMBC correlations were observed also between H-4 and C-2 and C-6 atoms. That the major component *trans*-**4a** possessed the *trans* configuration was based on the vicinal *J* constant values for the proton H-4 being larger for structure *trans*-**4a** (td, *J* = 9.5, *J* = 4.5 Hz) compared with those observed for the minor *cis*-3,4-disubstituted tetrahydropyran *cis*-**4a** (q, *J* = 3.5 Hz).

Following correspondence with Talipov in 2008,* he repeated the reaction between formaldehyde and 1-heptene in TFA, followed by neutralization with ammonia (the latter would be expected to cleave trifluoroacetates to alcohols). This gave a mixture of two compounds for which he kindly provided the ^{13}C NMR data, assigning them as *cis*- and *trans*-4-pentyl-3-hydroxytetrahydro*furan* (**6a**). We obtained essentially identical data following addition of ammonia at the end of the Prins reaction. The same data were obtained if the individual tetrahydropyranyl trifluoroacetates *trans*-**4a** and *cis*-**4a** underwent methanolysis in the presence of K_2CO_3, to give structures *trans*-**4b** and *cis*-**4b**. A comparison of this data with literature ^{13}C NMR data for 4-hydroxytetrahydropyrans[11,12] and 3-hydroxytetrahydrofurans[12,13] is given in Figure 1.

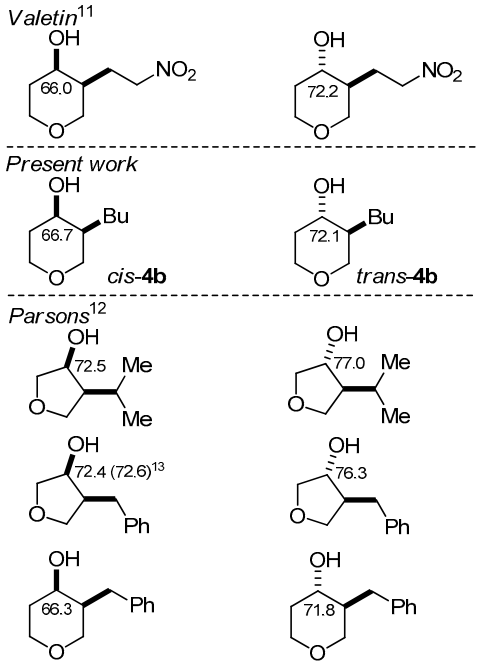


Figure 1. Comparison of selected ^{13}C NMR chemical shifts (in ppm) for 3-hydroxytetrahydrofurans and 4-hydroxytetrahydropyrans.

On analyzing the ^{13}C NMR data in Figure 1, it can been seen, in particular, that the chemical shifts of carbinol carbons are always greater than 70 ppm for 4-alkyl-3-hydroxytetrahydrofurans, with those of *trans*-isomers greater than 76 ppm. In contrast, the chemical shifts of carbinol carbons of 3-alkyl-4-hydroxytetrahydropyrans are ~66 and ~72 ppm for *cis*- and *trans*-isomers, respectively. This data comparison provides strong evidence that *cis*- and *trans*-4-butyl-3-hydroxytetrahydropyrans (**4a**) were prepared and not 3-hydroxytetrahydrofurans **6a**, and further implies that the process proceeds as in Scheme 2, not Scheme 3, and by analogy this pathway is likely for higher aldehydes in TFA as well.

Finally, the data for 3-alkyl-4-chlorotetrahydro'furans', obtained by Talipov as the additional products from the reaction of terminal olefins with formaldehyde and Me_3SiCl in TFA,[9] was compared with literature data[14] for a homologous 3-alkyl-4-chlorotetrahydropyran (Fig. 2). The literature data is consistent with the products reported by Talipov also being cyclic ethers with a six- and not five-membered ring.

* E-mail from Prof. R. F. Talipov, 13th February 2008.

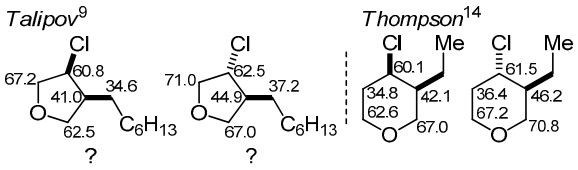


Figure 2. Comparison of selected ^{13}C NMR chemical shifts (in ppm) for 3-alkyl-4-chlorotetrahydro'furans' and -tetrahydropyrans.

In summary, Prins reactions of terminal alkenes with formaldehyde in trifluoroacetic acid produce substituted tetrahydropyrans, and not the erroneously reported 2,5-dihydrofurans or substituted tetrahydrofurans.

Experimental

IR spectra were obtained in film using a PerkinElmer FTIR spectrometer with universal ATR sampling accessory. ^1H, ^{19}F, and ^{13}C NMR spectra (400, 376, and 100 MHz, respectively), as well as ^1H–^1H COSY, DEPT–HSQC, and ^1H–^{13}C HMBC spectra were recorded on a Bruker Avance AVIIIHD 400 spectrometer in $CDCl_3$, referenced to residual $CHCl_3$ singlet at 7.26 ppm and to the central line of $CDCl_3$ triplet at 77.16 ppm for ^{13}C NMR spectra. ^{13}C NMR peaks were assigned by standard methods using HSQC. High-resolution mass spectra were obtained by electrospray ionization, using an Thermo Fisher Orbitrap Exactive mass spectrometer. Flash column chromatography was carried out using silica gel (VWR chemicals, BDH), monitored by thin-layer chromatography on Merck 60 F_{254} plates. TLC spots were visualized by immersion in $KMnO_4$, followed by heating.

Paraformaldehyde was dried overnight under high vacuum prior to use. 1-Heptene was freshly distilled from CaH_2. Trifluoroacetic acid (99%, extra pure) was used as received (Acros). Petroleum ether of bp 40–60°C was used in flash column chromatography.

***Trans*- and *cis*-3-butyltetrahydro-2*H*-pyran-4-yl 2,2,2-trifluoroacetate (*trans*- and *cis*-4a)**. The procedure and reaction scale of Talipov was followed.[5b] TFA (15 ml) was added to paraformaldehyde (5.00 g, 170 mmol), and the mixture heated until a clear solution formed (3–5 min). The mixture was cooled to room temperature, then 1-heptene (**3a**) (9.3 ml, 80 mmol) was added dropwise. After 3 h at room temperature, unreacted 1-heptene and TFA were removed by distillation (<40°C, ~100 mbar). The residue, a yellow oil (~11 g), was distilled at ~15 mbar and the fraction of bp 60–70°C (5.3 g, an impure 75:25 mixture of compounds *trans*-**4a** and *cis*-**4a**) further was purified by flash column chromatography (0–20% Et_2O in petroleum ether). First eluted compound *trans*-**4a**. Yield 3.2 g (19%), colorless liquid. R_f 0.26 (20% Et_2O in petroleum ether). IR spectrum, ν, cm^{-1}: 1139 (w), 1164 (s), 1222 (m), 1249 (s), 1781 (s), 2861 (w), 2934 (m), 2962 (m). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.0, CH_3); 1.14–1.34 (5H, m, 7-CH_a, 8,9-CH_2); 1.40–1.47 (1H, m, 7-CH_b); 1.71–1.79 (1H, m, 5-CH_a); 1.81–1.88 (1H, m, 3-CH); 2.02–2.08 (1H, m, 5-CH_b); 3.19 (1H, dd, *J* = 12.0, *J* = 9.0, 2-CH_a); 3.50 (1H, ddd, *J* = 12.0, *J* = 10.5, *J* = 3.0, 6-CH_a); 3.93–4.01 (2H, m, 2-CH_b, 6-CH_b); 4.87 (1H, td, *J* = 9.5, *J* = 4.5, 4-CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.9 (CH_3); 22.9 (C-9); 28.1 (C-7); 28.8 (C-8); 30.7 (C-5); 40.7 (C-3); 65.6 (C-6); 69.9 (C-2); 78.9 (C-4); 114.7 (q, J_{CF} = 286, CF_3); 157.3 (q, J_{CF} = 42, C=O). ^{19}F NMR spectrum, δ, ppm: –75.2. Found, *m*/*z*: 277.1023 $[M+Na]^+$. $C_{11}H_{17}O_3F_3Na$. Calculated, *m*/*z*: 277.1022. Second eluted compound *cis*-**4a**. Yield 0.89 g (5%), colorless liquid. R_f 0.2 (20% Et_2O in petroleum ether). IR spectrum, ν, cm^{-1}: 775 (m), 1031 (w), 1121 (m), 1158 (m), 1219 (m), 1781 (s), 2862 (w), 2933 (w), 2961 (w). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.0, CH_3); 1.18–1.33 (6H, m, 3CH_2); 1.84–1.98 (3H, m, 3-CH, 5-CH_2); 3.51 (1H, t, *J* = 11.0, 2-CH_a); 3.63–3.79 (3H, m, 2-CH_b, 6-CH_2); 5.32 (1H, q, *J* = 3.5, 4-CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.9 (CH_3); 22.8 (C-9); 26.5 (C-7); 28.7 (C-8); 30.1 (C-5); 39.2 (C-3); 63.0 (C-6); 67.8 (C-2); 74.9 (C-4); 114.7 (q, J_{CF} = 286, CF_3); 157.1 (q, J_{CF} = 42, C=O). ^{19}F NMR spectrum, δ, ppm: –75.1. Found, *m*/*z*: 141.1274 $[M–OCOCF_3]^+$. $C_9H_{17}O$. Calculated, *m*/*z*: 141.1274.

***Trans*- and *cis*-3-butyltetrahydro-2*H*-pyran-4-ol (*trans*- and *cis*-4b)**. The above procedure and reaction scale was followed, but after 3 h at room temperature, the mixture was neutralized by aq NH_3 (15 ml). The aqueous layer was extracted with Et_2O (2 × 30 ml), dried over Na_2SO_4, and evaporated under reduced pressure. The residue, a yellow oil (~8 g), was distilled at ~15 mbar and the fraction of bp 100–110°C (4.7 g, an impure 75:25 mixture of compounds *trans*- and *cis*-**4b**) further was purified by flash column chromatography (20–40% Et_2OAc in petroleum ether). First eluted compound *trans*-**4b**. Yield 1.72 g (17%), colorless liquid. R_f 0.3 (30% EtOAc in petrol). IR spectrum, ν, cm^{-1}: 626 (s), 1050 (s), 1080 (s), 1150 (s), 1222 (m), 1466 (m), 2856 (s), 2925 (s), 2955 (s), 3386 (br). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.0, CH_3); 1.03–1.13 (1H, m, 7-CH_a); 1.17–1.37 (4H, m, 8,9-CH_2); 1.43–1.62 (2H, m, 3-CH, 5-CH_a); 1.63–1.72 (1H, m, 7-CH_b); 1.73–1.92 (2H, m, 5-CH_b, OH); 3.02 (1H, t, *J* = 11.0, 2-CH_a); 3.35–3.44 (2H, m, 4-CH, 6-CH_a); 3.90–3.98 (2H, m, 2-CH_b, 6-CH_b). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 14.1 (CH_3); 23.2 (C-9); 28.3 (C-7); 29.3 (C-8); 35.3 (C-5); 44.6 (C-3); 66.5 (C-6); 70.6 (C-2); 72.1 (C-4). Found, *m*/*z*: 141.1272 $[M–OH]^+$. $C_9H_{17}O$. Calculated, *m*/*z*: 141.1273. Second eluted compound *cis*-**4b**. Yield 0.36 g (3%), colorless liquid. R_f 0.2 (30% EtOAc in petroleum ether). IR spectrum, ν, cm^{-1}: 626 (s), 1080 (s), 1150 (s), 1222 (m), 1466 (m), 2856 (s), 2927 (s), 2955 (s), 3389 (br). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.0, CH_3); 1.19–1.36 (6H, m, 3CH_2); 1.58 (1H, br. s, OH); 1.63–1.73 (2H, m, 3-CH, 5-CH_a); 1.77–1.86 (1H, m, 5-CH_b); 3.51–3.56 (2H, m, 2-CH_2); 3.64 (1H, ddd, *J* = 11.5, *J* = 4.5, *J* = 3.5, 6-CH_a); 3.78 (1H, td, *J* = 11.0, *J* = 3.0, 6-CH_b); 4.00 (1H, dt, *J* = 5.5, *J* = 3.0, 4-CH). ^{13}C NMR spectrum, δ, ppm: 14.1 (CH_3); 23.1 (C-9); 26.6 (C-7); 29.1 (C-8); 33.5 (C-5); 40.9 (C-3); 63.2 (C-6); 66.7 (C-4); 67.6 (C-2). Found, *m*/*z*: 141.1272 $[M–OH]^+$. $C_9H_{17}O$. Calculated, *m*/*z*: 141.1273.

***Trans*-3-butyltetrahydro-2*H*-pyran-4-ol (*trans*-4b)**. Compound *trans*-**4a** (250 mg, 0.98 mmol) was stirred with K_2CO_3 (270 mg, 1.96 mmol) in MeOH (1 ml) at room

temperature. After 3 h, the mixture was quenched with 10% HCl (1 ml) and extracted with EtOAc (2×5 ml). The combined organic layers were washed with brine (2 ml) and dried (Na_2SO_4). Evaporation under reduced pressure followed by chromatography (30% EtOAc in petroleum ether) gave a colorless liquid. Yield 138 mg (89%). The spectral data were identical to those of compound *trans*-**4b** obtained in one-pot procedure from 1-heptene (**3a**) and paraformaldehyde.

***Cis*-3-butyltetrahydro-2*H*-pyran-4-ol (*cis*-4b)**. Compound *cis*-**4a** (150 mg, 0.59 mmol) was stirred with K_2CO_3 (163 mg, 1.18 mmol) in MeOH (1 ml) at room temperature. After 3 h, the mixture was quenched with 10% HCl (1 ml) and extracted with EtOAc (2×5 ml). The combined organic layers were washed with brine (2 ml) and dried (Na_2SO_4). Evaporation under reduced pressure followed by chromatography (30% EtOAc in petroleum ether) gave a colorless liquid, *cis*-3-butyltetrahydro-2*H*-pyran-4-ol (*cis*-**4b**). Yield 87 mg (93%). The spectral data were identical to those of compound *cis*-**4b** obtained in one-pot procedure from 1-heptene (**3a**) and paraformaldehyde.

The Supplementary information file containing tabular comparisons of ^{13}C NMR data of compounds *trans*-**4a**, *cis*-**4a**, *trans*-**4b**, and *cis*-**4b** with that from Talipov's work and NMR spectra of compounds *trans*-**4a**, *cis*-**4a**, *trans*-**4b**, and *cis*-**4b** is available at the journal website at http://link.springer.com/journal/10593.

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