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A Novel One-Step Synthesis of γ-Lactones from Olefins and Phenyliodonium(ethoxycarbonyl)nonafluorobutylsulfonylmethanide Catalyzed by Copper(II) Triflate

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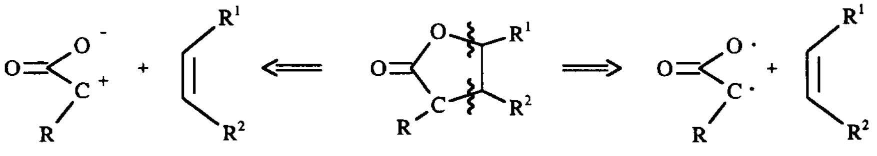
Abstract: The reaction of phenyliodonio(ethoxycarbonylnonafluorobutylsulfonyl)methanide (**4**) with alkenes **2** in the presence of copper(II) triflate affords γ-butyrolactones **7** in good yields.

α-Substituted γ-lactones **3** are important intermediates in the synthesis of bioactive products.[1] An interesting retrosynthetic analysis of γ-lactones is the disconnection shown in Scheme 1. The monomethyl ester of malonic acid and cyanacetic acid have been employed as synthetic equivalent of the synthon **1B** to obtain the corresponding γ-lactones **3** (R = CO_2Me or CN) by sonochemical lactonization in the presence of olefins **2** promoted by $Mn(OAc)_3$ or ceric ammonium nitrate.[2]

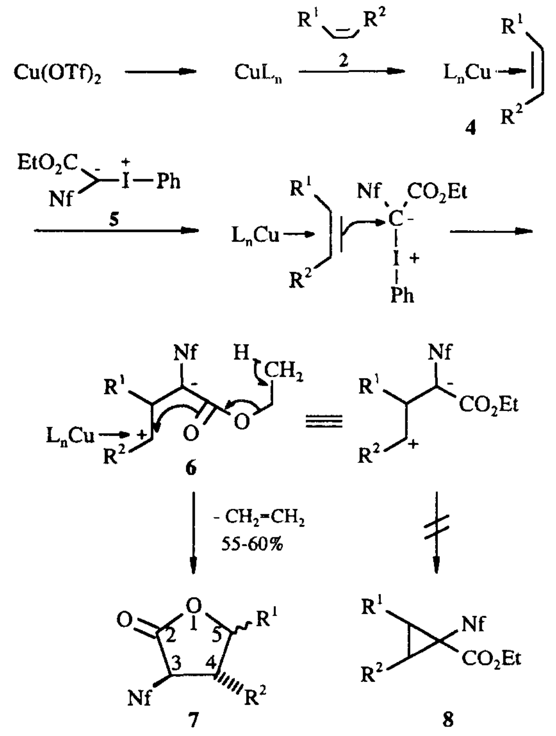
Herein we report a convenient synthesis of α-nonafluorobutylsulfonyl(nonaflyl) γ-lactones **7** with high stereospecificity at the C-3 and C-4 (only the *trans*-isomers were found), starting from the sulfonyl ylide **4** as the synthetic equivalent of the synthon **1A**. The lactones **7** are advantageous intermediates due to the ambivalent function of the nonaflyl moiety as an electrophile or as a nucleofuge leaving group.[3]

Scheme 1:



As part of our studies on perfluoroalkyl sulfones, we have synthesized several perfluoroalkylsulfonyl substituted ylides and examined their properties, e.g. in generating the corresponding sulfonyl carbenes.[4] The formation of a cyclopropyl derivative was achieved by decomposition of a phenyliodonium(cyanononafluorobutylsulfonyl)methanide[4] as compared to the bis(perfluoroalkylsulfone) derivatives.[5] The substitution of one perfluoroalkanesulfonyl group by a cyano group in the latter increased the reactivity of the sulfonyl ylide. We envisaged that the substitution of the cyano group in phenyliodonium(cyanononafluorobutylsulfonyl)methanide[4] by an ester group will have much higher effect of destabilization of the negative charge conferring a higher reactivity. Accordingly, we have studied the decomposition of phenyliodonio(ethoxycarbonylnonafluorobutylsulfonyl)methanide (**4**) with various olefins in the presence of copper(II) triflate. Ylide **4** was prepared by reaction of ethyl (nonafluorobutylsulfonyl)acetate with diacetoxy iodobenzene in 40-50% yield (Scheme 2).[6] The reaction of ylide **4** with alkenes **2** in the presence of $Cu(OTf)_2$ afforded the α-nonafluorobutanesulfonyl lactones **7** (Scheme 2).[7] In the absence of $Cu(OTf)_2$, the reaction of alkenes **2** with ylide **4** gives products resulting from reductive alkylation of alkenes **2**.[8] Scheme 2 gives a possible explanation for the formation of the γ-lactones **7**. $Cu(OTf)_2$ is first reduced to Cu(I) as known for many catalytic reactions[9] by the initial formation of a copper-olefin-π-complex **5**. The electron rich character of copper(I) complexes **5** enhances the nucleophilic character of olefins. Thus **5** attacks at the carbon atom of the sulfonyl ylide **4** with elimination of iodobenzene and formation of the σ-copper complex **6**. The Cu(I) stabilizes the positive charge and the nonaflyl group the negative charge of the zwitter ion **6**. The carbonyl oxygen eliminates the copper catalyst and the γ-lactone is formed by transfer of a proton from the ethyl group of the ester on the negative carbon atom with subsequent elimination of ethene. While no cyclopropanated product **8** was detected, the elimination of ethene to give the lactone **7** is faster than the cyclization to **8** (Scheme 2).

Scheme 2:

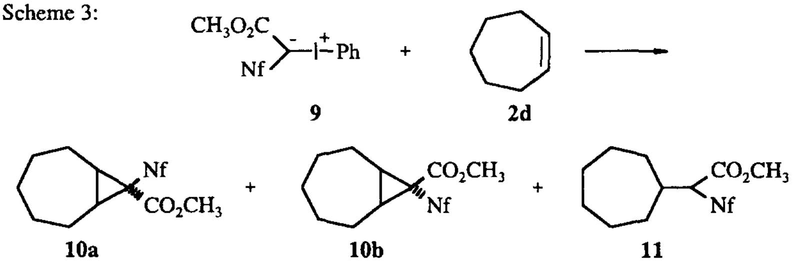


2,6	R¹	R²
a	$-(CH_2)_3-$	
b	$-(CH_2)_4-$	
c	$-(CH_2)_5-$	
e	C_4H_9	H
f	C_2H_5	CH_3

7	R¹	R²	yield (%)
a	$-(CH_2)_3-$		65
b	$-(CH_2)_4-$		60
c	$-(CH_2)_5-$		65
d	α-C_4H_9	H	52 (1.2:1)
e	β-C_4H_9	H	
f	α-C_2H_5	CH_3	52
g	β-C_2H_5	CH_3	
h	α-CH_3	C_2H_5	50
i	β-CH_3	C_2H_5	

Support for this mechanism is obtained by using the methyl instead of ethyl ester of the sulfonyl ylide **4**. Thus, in the case of the methoxycarbonyl ylide **9**, which cannot undergo elimination of ethene, the reaction yields a mixture of cyclopropane derivatives **10a** and **10b** and the cycloheptyl compound **11**, formed by reductive alkylation[8] (Scheme 3).

Scheme 3:



The zwitterion **6** seems to be a relatively long-living species, so that the C_4-C_5 bond can rotate (in the case of acyclic olefins) before cyclization takes place. Thus reaction of ylide **4** with (*Z*)-pent-2-ene (**2e**) affords a mixture of *cis/trans* isomers **7f,g** and **7h,i**. In all the lactones obtained, the nonaflyl group is positioned *trans* to the neighbouring substituent R^2, probably due to steric reasons. All the products obtained were characterized by IR, MS, ^1H, and ^{13}C NMR spectra.[10] The relative configuration of **7h,i** was determined by NOE-^1H NMR. Moreover the structure of γ–lactone **7b** was determined by X-ray crystallography (Figure).[11]

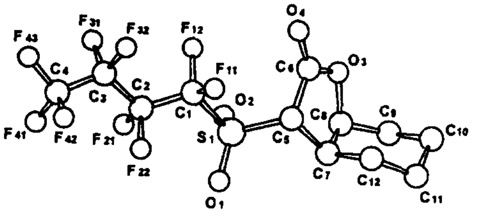


Figure. X-ray Structure of 7b

In summary, the copper catalysed reaction of the iodine ylide **4** with alkenes **2** is an excellent procedure for the synthesis of a functionalized γ–lactone moiety with a 3-substituted nonaflyl group, a synthetically important species. Further work on the stereochemical outcome of the reaction is in progress.

References and Notes

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6. **Phenyliodonium(ethoxycarbonylnonaflyl)methanide** (**4**): To a solution of ethyl nonaflylacetate (4 mL, 16.9 mmol) in CH_2Cl_2 (150 mL) was added iodobenzene diacetate (5.4 g, 16.4 mmol) and stirred for 3 h at r.t. The CH_2Cl_2 solution was washed with aq sat. $NaHCO_3$ and frozen immediately to -30°C. The crystallized product was filtered; yield: 3.9 g - 4.8 g (40-

50%); mp 98-99°C (dec). The product can be stored under Et$_2$O as a suspension for several weeks at -30°C. IR (KBr): *m* = 1668 (C=O), 1353, 1340 (SO$_2$), 1254, 1236 cm^{-1} (CF). ^{1}H NMR (250 MHz, CD$_3$CN/TMS): *δ* = 1.19 (t, 3H, *J* = 7.1 Hz, CH$_3$), 4.11 (q, 2H, *J* = 7.1 Hz, OCH$_2$), 7.46-7.93 (m, 5H, C$_6$H$_5$). ^{13}C NMR (62.9 MHz, CD$_3$CN/TMS: 14.8, 54.5, 62.3, 132.5, 133.1, 134.4, 164.6. MS= *m/z* (%) = 527 (M$^+$, <1).

7. **Copper Triflate Catalysed Reaction of Iodine Ylide 4 with Olefins; General Procedure:** A mixture of the ylide (**4**; 2-3 mmol) and copper triflate (0.4 mmol%) in the appropriate olefin **2** (80 mL) was heated to 45°C till the solid material had dissolved (ca. 4 h). The olefin was removed under vacuum and the crude product was prepurified by column chromatography on silica gel. Iodobenzene was removed by eluting with hexane and the product mixture was eluted out with Et$_2$O. The product mixture was separated by preparative TLC (CHCl$_2$/hexane, 1:2.5).
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10. Selected spectroscopic data: **7a** mp 101-102°C. IR (KBr): *m* = 1774 (C=O), 1369, 1354 (SO$_2$), 1236, 1204, 1192 cm^{-1} (CF). ^{1}H NMR: *δ* = 1.63-1.81 (m, 3H), 2.05-2.16 (m, 3H), 3.40-3.48 (m, 1H), 4.19 (m, 1H), 5.14 (dt, *J* = 5.86, 1.82 Hz). ^{13}C NMR: *δ* = 23.2, 32.3, 32.9, 40.2, 68.6, 86.3, 164.7. MS: *m/z* (%) = 409 (M$^+$, 0.1). **7b**: mp 127-128°C. IR (KBr): *m* = 1771 (C=O), 1369, 1354 (SO$_2$), 1232, 1204, 1180 cm^{-1} (CF). ^{1}H NMR: *δ* = 1.30-1.64 (m, 4H), 1.69-1.80 (m, 2H), 1.86-1.98 (m, 1H), 2.11-2.23 (m, 1H), 3.11-3.18 (m, 1H), 4.04 (s, 1H), 4.94 (q, 1H, *J* = 3.99 Hz). ^{13}C NMR: *δ* = 18.9, 22.8, 26.7, 27.2, 37.2, 68.5, 79.1, 164.7. MS: *m/z* (%) = 423 (M$^+$,2). **7d** + **7e**. (~1.2:1). IR (KBr): *m* = 1774 (C=O), 1369, 1354 (SO$_2$), 1236, 1217, 1167 (CF). ^{1}H NMR (400 MHz, CDCl$_3$/TMS): *δ* = 0.84-0.88 (2t, CH$_3$), 1.28-1.41, 1.62-1.80 [m, (CH$_2$)$_3$ of butyl], 2.33-2.39, 2.78-2.84 (m, H-4b), 2.41-2.49, 2.96-3.02 (m, H-4a), 4.42 (t, J = 10, 3.3 Hz, H-3), 4.57 (t, *J* = 10 Hz, H-3), 4.47-4.54, 4.68-4.75 (m, H-5). ^{13}C NMR: *δ* = 13.7, 22.2, 27.0, 29.7, 29.9 (C$_4$F$_9$), 34.8, 35.0 (C-4), 61.7, 62.2 (C-3), 79.2, 80.7 (C-5), 164.1, 164.2 (C-2). MS: *m/z* (%) = 425 (M$^+$, 15). The reaction with *cis*-pent-2-ene gave 4 isomers, separated by TLC into two pure isomers **7g** and **7i**. **7f** and **7h** were obtained as an inseparable mixture. The structures were determined by NOE experiments conducted on the H-3,4,5 protons. As an example the data for **7i** is given. **7i**: IR (KBr): *m* = 1786 (C=O), 1375, 1352 (SO$_2$), 1238, 1217 (CF). ^{1}H NMR: *δ* = 1.02 (t, 3H, *J* = 7.44 Hz, CH$_2$CH$_3$), 1.53 (d, 3H, *J* = 6.33 Hz, CH$_3$), 1.72-1.85 (m, 2H, CH$_2$CH$_3$), 2.75 (quintet, 1H, *J* = 6.33 Hz, H-4), 4.30 (dd, 1H, *J* = 7.39, 1.15 Hz, H-3), 4.44 (quintet, 1H, *J* = 6.16 Hz, H-5). ^{13}C NMR: *m* = 9.5, 17.3, 26.7, 37.2, 68.7, 86.9, 164.2. MS: *m/z* (%) = 821 (M^+_2, 0.4), 411 (M$^+$, 11). The ^{1}H NMR and ^{13}C NMR were recorded in CDCl$_3$/TMS at 250 and 62.9 MHz, respectively.
11. We thank Dr. C. Maichle-Mössner for the X-ray structure of **7b**. The full data for the X-ray crystal structure have been deposited at the Cambridge Crystallographic Data Centre.

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