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A structure–taste study of arylsulfonyl(cyclo)alkanecarboxylic acids

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Abstract—A number of sweeteners contain a sulfonyl group. In our current search for new glucophores several new compounds containing such group were obtained. A series of novel 1-phenylsulfonylcyklohexanecarboxylic acids and 2-arylsulfonylalkanecarboxylic acids was obtained and evaluated for their sweet taste quality. It has been found that methyl substituents are of the key importance for the activity of these compounds.

1. Introduction

Synthetic sweeteners are appreciated by industry that needs such substances for dietary applications. Acesulfame K, saccharin, cyclamate (Chart 1) are well known synthetic sweeteners that are used in large quantity, but their taste quality are still far from the ideal sucrose profile.

Designing, discovering, and developing novel active compounds are far from trivial. Compared to the design of a new pharmaceutical, which is extremely complicated, developing a new sweetener can be even more difficult. The reasons for this are quite obvious. The use of pharmaceuticals is usually restricted to a certain group of patients that use them in small doses. Frequently, even if it is in some sense risky, it is better to take them than to die from the disease. On the contrary, sweeteners must not only be of excellent taste but they should also be absolutely safe for the consumption by a wide range of people. Many different classes of compounds have been reported to elicit sweet taste. A number of them contain a sulfonyl group. In particular, similar sulfur systems can be found especially in sweeteners that are of commercial importance.

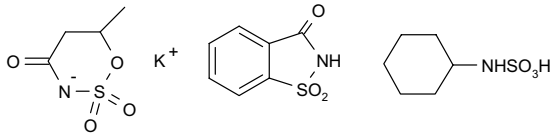

Chart 1. Acesulfame K, saccharin, cyclamate.

In our previous researches we have found that some 1-arylsulfonylalkanecarboxylic acids and 1-arylsulfonylcycloalkanecarboxylic acids (ASA) are potent sweeteners having the activity similar to those of the saccharin or aspartame.[1] In our current work we concentrated on the design and synthesis of new analogs containing sulfonyl group.

2. Concept of the drug design

The requirements for sweet taste induction have been deduced by a comparison of different sweetener series to give several sweet taste receptor models. An early Shallenberger theory that based sweetness on two-point concerted hydrogen AH–B bonding[2] has been supplemented by the Kier's AH, B, X model[3] that involves the hydrophobic interaction site. A discovery of hypersweeteners brought the Multipoint Attachment Theory (MPA) of Tinti–Nofre that includes eight interaction sites, described by B, AH, XH, G1, G2, G3, G4 and D.[4] More recently, several studies attempted to construct multi-class QSAR or QSPR sweetness models.[5,6]

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On the other hand, a structure of the sweet taste receptor has been described as a polypeptide chain having seven transmembrane domain segments, TMI–TMVII which form a pocket in which sweet ligands are bound.[7,8]

Discovering drugs is a complicated issue that lacks general approach. Basically, an efficient technology together with a precise knowledge of the real or possible ligand–receptor interactions should make drug discovery a dead certainly. However, it is not a fact and the analysis of the SAR by screening receptor ligands is still an important design strategy even in these cases when we have 3D receptor data. Paradoxically, so called fragment approach that insists on the importance of the certain two-dimensional molecular frameworks for the drug-likeness and lead generation has just appeared.[9] Therefore, we followed similar strategy in our study.

Chart 2 illustrates the basic structure–taste-regularities in the series of arylsulfonylalkanoic acids (ASA) obtained and tested in previous studies. Thus, besides parent compound **1**[10], most of the active analogs are found among acyclic forms **2** and **3** that are mostly C_α-alkyl-monosubstituted acids **2**.[1,10–15] However, this rule is not general, which means that neither all monosubstituted compounds are active, nor all disubstituted are inactive, for example, compound **3** appeared to taste sweet. More recently we have also found that the replacement of the carboxylic function by amide or tetrazole moiety resulted in the loss of sweet activity; however, the compounds are active bitter tastants.[16]

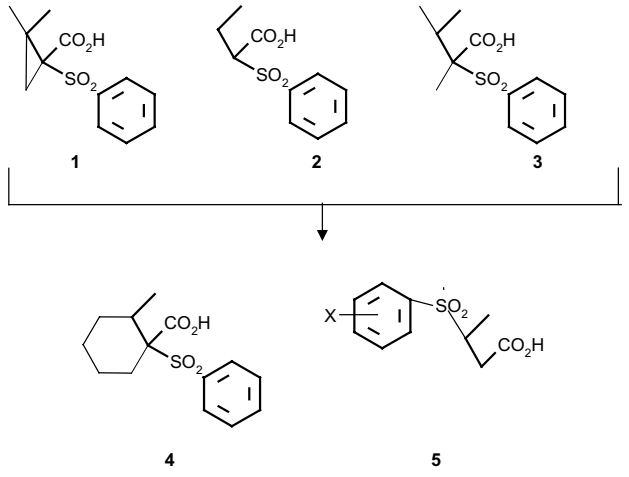
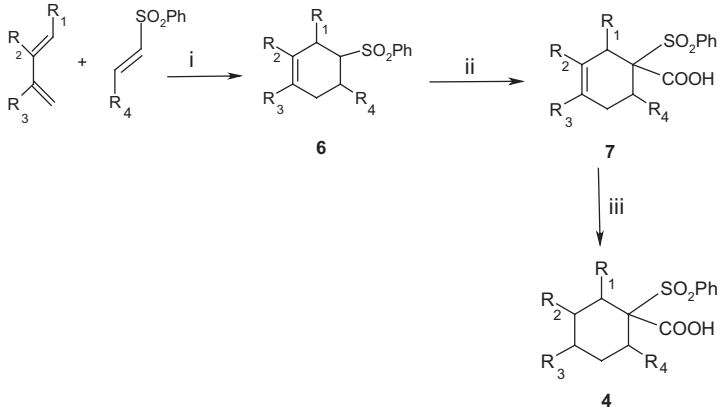


Chart 2. Design of arylsulfonyl(cyclo)alkanecarboxylic acids **4** and **5**.

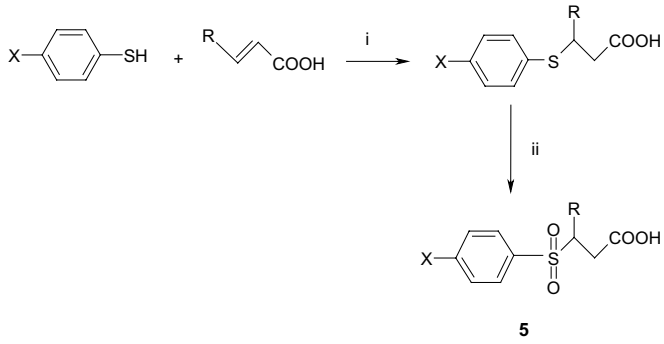
As a first attempt we designed 1-cycloalkanecarboxylic acids **4** whose cycle was conceived as the result of superimposition of the active parent or acyclic structures having 2-methyl substituent (Chart 2). Our hypothesis that the inclusion of such a group would afford compounds retaining sweet taste was supported by molecular modeling investigations. This shows that in fact two alkyl substituent can favor similar conformational profiles for active compounds, which has also been proved by the X-ray structures and 3D QSAR analysis.[17] The only active cyclic structure found among ASA compounds is a parent compound **1**. By removing 2-dimethyl substituents in the parent structure **1** or 4, 5 or 6-member analogs we obtained nonsweet compounds.[1] These data suggest that the methyl substitution at the C_2 atom is of the key importance for the activity of phenylsulfonylcycloalkanecarboxylic analogs **4**. We speculated also that the hydrophobic interactions of the 2-methyl group could explain the activity. At the same time a question comes how important is the distance between carboxylic function and sulfonyl group. Therefore, we also obtained a series of 2-arylsulfonylalkanecarboxylic acids (3-arylsulfonylbutanoic acids) **5** to test the affect of the extension of the distance between the carboxyl and arylsulfonyl functions on the compound activity. Formally, a chain of these compounds also contains 2-methyl group.

3. Chemistry

Cyclohexane analogs **4** were obtained by the Diels–Alder cycloaddition as shown in Scheme 1. We used the reaction similar to those of the Paquette for the cyclization of phenyl vinyl sulfone and butadiene.[18] This gave unsaturated cyclohexene sulfones **6**. Carboxylation of



Scheme 1. Reagents and conditions: (i) method A: benzene, hydroquinone, 120–135 °C (22–28 h), method B: xylene, 30 min; (ii) *n*-BuLi, CO_2, H^+/H_2O; (iii) CH_3OH, H_2, Pt/C.



Scheme 2. Reagents and conditions: (i) Et_3N, THF, 0 °C; (ii) CH_3COOH, 30% H_2O_2.

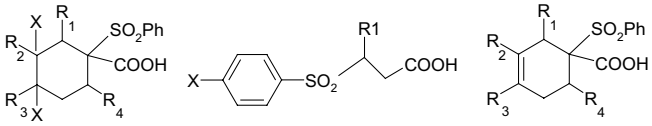
cyclohexene sulfones by the treatment of *n*-BuLi and CO_2 gave 1-phenylsulfonylcyclohexenecarboxylic acids **7**, respectively, and the hydrogenation of **7** with hydrogen provides a variety of 1-phenylsulfonylcyklohexanecarboxylic acids **4** of the different methyl-substitution pattern. 2-Arylsulfonylalkanecarboxylic acids **5** were prepared in the reaction of thiophenols with the, α,β-unsaturated acids in Et_3N/THF similarly to the previously reported synthesis of Yoonmo and Cohen.[19] The resulted 2-phenyltioalkanecarboxylic acids were oxidized by 30% H_2O_2 in acetic acid (Scheme 2).

4. Results and discussion

2,4-Dimethyl-1-phenylsulfonylcyklohexanecarboxylic acid **4f** appeared to be the only active compound among compounds **4**. This means that a double methyl substitution is needed in the cyclohexane ring to elicit sweet taste of compounds **4**. Quite surprisingly, a majority of the synthetic precursors of **4**, that is, 2-methyl-1-cyklohexenecarboxylic acids **7** are potent sweet tastants, including single 2-methyl group substituted analog **7c**. Moreover pure sweet taste was observed for active compounds **4** and **7**. Sweet taste threshold concentrations range from 0.750 to 0.500 mmol/L (Table 1). This compares advantageously to the recognition threshold values of sucrose (10–12 mmol/L) or cyclamate (1–3 mmol/L), but is higher than the respective values for saccharin (0.015–0.030 mmol/L), acesulfame K (0.070–0.130 mmol/L)[20] or the parent compound **1** (0.250 mmol/L).[15]

2,4-Dimethyl-unsaturated analog **7f** appeared to be the most active among all newly synthesized compounds. Thus 2,4-dimethyl location seems to be optimal eliciting sweetness both in cyclohexane **4** and cyclohexene **7** series. An alternative introduction of the methyl groups in position R_3 and R_4 does not deprive compound **7d** of their sweet taste activity; however, similar compound **4d** is inactive. It is worth noticing that also a substitution of three cyclohexene ring hydrogens with methyl groups (compound **7e**) generates an active molecule, while similar cyclohexane analog **4e** is inactive. These regularities seems to indicate, that methyl group can interact with the receptor as an important part of hydrophobic moiety. We believe the inactivity of **4** in comparison to the activity of **7** can be explained by steric hindrance during sweet tastant–receptor interactions. The rich methyl substitution pattern within cyclohexane ring generated a bulky molecule, in contrary, double bond molecule that is much more flat evoked sweet taste. In turn, almost all 2-phenylsulfonylalkanecarboxylic (3-phenylsulfonylalkanoic) acids appeared to be inactive and bitter. Acid **5e** is the only exclusion, as this compound has been reported to have sweet and bitter taste. Interestingly, also this molecule includes two methyl groups, that is β-methyl and aromatic methyl substituent. The inactivity of the Cl-arylog **5b** clearly implies

Table 1. Taste of acids **4**, **5**, **7**



Compound	R_1	R_2	R_3	R_4	X	Taste/C_{sw} [mmol/L][a]
4a	H	H	H	H	H	Inactive
4b	H	H	CH_3	H	H	Inactive
4c	H	H	H	CH_3	H	Inactive
4d	H	H	CH_3	CH_3	H	Inactive
4e	H	CH_3	CH_3	CH_3	H	Inactive
4f	H	CH_3	CH_3	H	H	0.625[b]
5a	CH_3	—	—	—	Br	Inactive
5b	CH_3	—	—	—	Cl	Bitter
5c	CH_3	—	—	—	H	Inactive
5d	H	—	—	—	CH_3	Bitter
5e	CH_3	—	—	—	CH_3	0.750 Sweet-bitter
5f	H	—	—	—	H	Bitter
7a	H	H	H	H	—	Inactive
7b	H	H	CH_3	H	—	0.750[b]
7c	H	H	H	CH_3	—	0.750[b]
7d	H	H	CH_3	CH_3	—	0.750[b]
7e	H	CH_3	CH_3	CH_3	—	0.625[b]
7f	H	CH_3	CH_3	H	—	0.500[b]

[a] Measured using the Belitz double blind test.[20] The panel consisted of four members. A person not participating in the tests encoded all compounds. The recognition threshold values were estimated by testing 1 mL portion of the samples of decreasing concentration. Each concentration was encoded with two samples of tap water. The lowest concentration for which the judgments of the panelists are correct is then averaged.

[b] Pure sweet taste without any aftertaste.

hydrophobic interactions of the methyl group. This suggests that the methyl groups form important hydrophobic binding sites for sweet taste glucophore in the obtained series. Moreover, the inactivity of the majority of compounds **5** indicates that sulfonyl and carboxylic functions are fundamental pharmacophoric elements that are of the crucial importance for the compound sweetness.

5. Conclusions

In summary a potent series of alternative sweeteners have been identified. The analysis of the SAR regularities for the series indicates that the methyl substituents in 1-(cyklo)alkanecarboxylic acids are of the key importance for the activity of the new compounds synthesized.

6. Experimental

General procedure

6.1. 3-Arylsulfonylalkanoic acids 5

The unsaturated acid (0.050 molar equiv) was added dropwise to a solution of thiophenol (0.051 molar equiv) and triethylamine (0.055 molar equiv) in THF (7.5 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature, stirred overnight, quenched with 5% HCl (38 mL), and extracted with ether. The combined ether layer was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation to give the respective adducts.

A 30% H_2O_2 (5 mL) in CH_3COOH (2.5 mL) was added with stirring to the obtained adduct (0.015 molar equiv). The reaction mixture was stirred overnight, heated at 60–80 °C for 4 h, poured into water (15 mL) and extracted with CH_2Cl_2. Organic phase was washed with 5% $Na_2S_2O_3$, water, dried over $MgSO_4$ and evaporated.

6.1.1. 3-(*p*-Bromophenylosulfonyl)butanoic acid (5a). (25% yield). ^{1}H NMR [$(CD_3)_2CO$] δ 1.30 (d, 3H), 2.45 (q, 2H), 2.95 (q, 2H), 3.65 (m, 1H), 5.90 (s, –OH), 7.65–8.00 (m, Ar). IR (KBr) [cm^{-1}] 3340–2905 (OH); 1694 (C=O); 1312 (SO_2); 1136 (SO_2). AE: calcd C, 39.10; H, 3.61; found: C, 39.09; H, 3.56.

6.1.2. 3-(*p*-Chlorophenylosulfonyl)butanoic acid (5b). (11% yield). ^{1}H NMR [$(CD_3)_2CO$] δ 1.30 (d, 3H), 2.40 (q, 2H), 2.90 (q, 2H), 3.60 (m, 1H), 5.56 (s, –OH), 7.60–8.05 (m, Ar). IR (KBr) [cm^{-1}] 3400–2906 (OH); 1693 (C=O); 1313 (SO_2); 1137 (SO_2). AE: calcd C, 45.72; H, 4.22; found: C, 45.73; H 4.24.

6.1.3. 3-Phenylosulfonylbutanoic acid (5c). (52% yield). Mp = 102 °C, lit. mp = 102.5–103.5 °C.[21]

6.1.4. 3-(*p*-Tolilosulfonyl)propionic acid (5d). (38% yield). Mp = 95 °C, lit. mp = 113–114 °C.[22]

6.1.5. 3-(*p*-Tolilosulfonyl)butanoic acid (5e). (69% yield). Mp = 134 °C, lit. mp = 133.5–134 °C.[23]

6.1.6. 3-Phenylsulfonylpropionic acid (5f). (24% yield). Mp = 123 °C, lit. mp = 124–125 °C.[24]

6.2. Phenylsulfonylcyclohex-3-enes 6

6.2.1. Method A. A mixture of phenyl vinyl sulfone or phenyl-1-propenyl sulfone (0.0035 molar equiv), dienofile (1,3-diene) (0.0033 molar equiv), benzene (5 mL), and hydroquinone (15 mg) was heated in an evacuated Carius tube at 120–135 °C for 22–28 h. The crude isolated product was eluted through silica gel with 20% ethyl acetate in hexane. The recovered colorless, crystalline solid was used without further purification.

6.2.2. Method B. A mixture of sulfolene (0.017 molar equiv), phenyl vinyl sulfone or phenyl-1-propenyl sulfone (0.012 molar equiv) and xylene (2 mL) was shaken in a closed flask. After 30 min xylene was evaporated and a crude product was crystallized from benzene.

6.2.3. 1-Phenylsulfonylcyclohex-3-ene (method B). (76% yield). Mp = 74–76 °C, ^{1}H NMR ($CDCl_3$) δ 1.9 (m, 2H), 2.3 (m, 2H), 3.7 (m, 1H), 5.4 (m, 1H), 5.9 (m, 1H), 7.5–7.9 (m, 5H). AE: calcd C, 64.84; H, 6.35; found: C, 64.56; H, 6.82.

6.2.4. 1-Phenylsulfonyl-3,4-dimethylcyclohex-3-ene (method A). (76% yield). Mp = 79–81 °C, lit. mp = 79.5–81 °C.[18]

6.2.5. 1-Phenylsulfonyl-4-methylcyclohex-3-ene (method A). (80% yield). Mp = 74 °C lit. mp = 79 °C.[18]

6.2.6. 1-Phenylsulfonyl-6-methylcyclohex-3-ene (method B). (71% yield). Mp = 77–78 °C, ^{1}H NMR ($CDCl_3$) δ 1.21–1.24 (d, 3H), 1.62–1.69 (m, 1H), 2.0–2.07 (m, 1H), 2.34–2.44 (m, 1H), 7.50–7.71 (m, 3H), 7.86–7.92 (m, 2H), 8.60 (s, 1H). MS 236 $(M^+H)^+$. AE: calcd C, 66.63; H, 7.99; found: C, 67.09; H, 7.64.

6.2.7. 1-Phenylsulfonyl-3,4,6-trimethylcyclohex-3-ene (method A). (74.9% yield). Mp = 81–82 °C, ^{1}H NMR ($CDCl_3$) δ 0.6 (d, 3H), 1.60 (d, 2 × 3H), 1.8 (d, 2H), 2.5 (m, 2H), 3.4 (m, 1H), 3.8 (m, 1H), 7.60–8.0 (m, 5H). MS 264 $(M^+H)^+$. AE: calcd C, 68.14; H, 7.62; found: C, 67.98; H, 7.46.

6.2.8. 1-Phenylsulfonyl-4,6-dimethylcyclohex-3-ene (method A). (74.3% yield). Mp = 79–81 °C, ^{1}H NMR ($CDCl_3$) δ 0.6 (d, 3H), 1.63 (s, 3H), 1.8 (d, 2H), 2.0 (m, 2H), 3.4 (m, 2H), 5.8 (m, 1H), 7.6–8.0 (m, 5H). MS 250 $(M^+H)^+$. AE: calcd C, 67.63; H, 8.32; found: C, 67.31; H, 7.99.

6.3. Phenylsulfonylcyclohexenocarboxylic acids 7

A solution of sulfone (0.011 molar equiv) in 80 mL of dry diethyl ether in an argon atmosphere protected from external moisture was cooled externally to 5 °C. A solution of butyllithium in hexane (15.5 mL of 1.6 M solution) was added with stirring during 10 min. The mixture temperature rose during the addition. After

the additional 10 min of stirring with external ice bath cooling, the milky-yellow reaction mixture was added to about 100 g of crushed solid carbon dioxide, stirred, and then poured into a shallow dish open to air. Next day the residue was dissolved in warm water, and extracted two times with benzene, 10% NaOH, acidified with HCl, and extracted three times with methylene chloride. The organic layer was dried over $MgSO_4$, and concentrated by evaporation.

6.3.1. 1-Phenylsulfonyl-3-cyclohexenecarboxylic acid (7a) (method B). (54.4% yield). Mp = 171–177 °C, ^{1}H NMR ($CDCl_3$) δ 2.1–3.2 (3 × m, 6H), 5.8 (m, 1H), 6.1 (m, 1H), 7.6–8.2 (m, 5H). MS 267 $(M^+ H)^+$. AE: calcd C, 58.63; H, 5.30; found: C, 58.86; H, 5.46.

6.3.2. 1-Phenylsulfonyl-4-methyl-3-cyclohexenecarboxylic acid (7b). (57% yield). Mp = 182–184 °C, ^{1}H NMR ($CDCl_3$) δ 1.6 (s 3H), 2.0–3.3 (m, 6H), 5.6 (m, 1H), 7.6–8.0 (m, 5H). MS 281 $(M^+ H)^+$. AE: calcd C, 59.98; H, 5.75; found: C, 60.16; H, 5.62.

6.3.3. 1-Phenylsulfonyl-6-methyl-3-cyclohexenecarboxylic acid (7c) (method B). (53.9% yield). Mp = 197–199 °C ^{1}H NMR ($CDCl_3$) δ 1.6 (d, 2 × 3H), 2.1–3.2 (m, 6H), 7.6–8.0 (m, 5H). MS 281 $(M^+H)^+$. AE: calcd C, 59.98; H, 5.75; found: C, 59.64; H, 5.49.

6.3.4. 1-Phenylsulfonyl-4,6-dimethyl-3-cyclohexenecarboxylic acid (7d). (51% yield). Mp = 225–226 °C ^{1}H NMR ($CDCl_3$) δ 1.4 (d, 3H), 1.6 (s, 3H), 1.9–3.3 (m, 5H), 5.6 (d, 1H), 7.6–8.0 (m, 5H). MS 295 $(M^+ H)^+$. AE: calcd C, 61.20; H, 6.16; found: C, 60.87; H, 5.97.

6.3.5. 1-Phenylsulfonyl-3,4,6-trimethyl-3-cyclohexenecarboxylic acid (7e). (40% yield). Mp = 230–231 °C ^{1}H NMR ($CDCl_3$) 1.3 (d, 3H), 1.6 (d, 2 × 3H), 2.0–3.2 (m, 5H), 7.6–8.2 (m, 5H). MS 309 $(M^+H)^+$. AE: calcd C, 62.31; H, 6.54; found: C, 61.96; H 6.18.

6.3.6. 1-Phenylsulfonyl-3,4-dimethyl-3-cyclohexenecarboxylic acid (7f). (54% yield). Mp = 221–223 °C ^{1}H NMR ($CDCl_3$) δ 1.6 (d, 2 × 3H), 2.1–3.2 (m, 6H), 7.6–8.0 (m, 5H). MS 295 $(M^+H)^+$. AE: calcd C, 61.20; H, 6.16; found: C, 61.16; H, 6.17.

6.4. Phenylsulfonylcyclohexanecarboxylic acids 4

Hydrogen was inserted to a mixture of 7.5 mL dry methanol and palladium 10% on charcoal (100 mg) at room temperature for 20 min. After that time unsaturated acid (0.5 g) in 3 mL dry methanol was injected through the syringe and hydrogen was passed for the additional 10–30 min. The catalyst was removed by filtration, and the solvent was evaporated. Crude product was crystallized from pentane.

6.4.1. 1-Phenylsulfonylcyclohexanecarboxylic acid (4a). (80% yield). Mp = 156 °C, lit. mp = 156–158 °C.[11]

6.4.2. 1-Phenylsulfonyl-4-methylcyclohexanecarboxylic acid (4b). (80% yield). Mp = 89–90 °C ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 3H), 1.6–2.8 (m, 6H), 7.6–8.2 (m, 5H).

6.4.3. 1-Phenylsulfonyl-2-methylcyclohexanecarboxylic acid (4c). (90% yield). Mp = 112–114 °C ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 3H), 1.3–2.8 (m, 9H), 7.6–8.2 (m, 5H).

6.4.4. 1-Phenylsulfonyl-2,4-dimethylcyclohexanecarboxylic acid (4d). (86% yield) Mp = 99–101 °C ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 3H), 1.3 (d, 3H), 1.6–2.8 (m, 6H), 7.6–8.2 (m, 5H).

6.4.5. 1-Phenylsulfonyl-2,4,5-trimethylcyclohexanecarboxylic acid (4e). (90% yield). Mp = 123–125 °C ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 2 × 3H), 1.2 (d, 3H), 1.6–2.8 (m, 6H), 7.6–8.2 (m, 5H).

6.4.6. 1-Phenylsulfonyl-3,4-dimethylcyclohexanecarboxylic acid (4f). (80% yield). Mp = 67–71 °C ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 2 × 3H), 1.4 (m, 2 × 1H), 2.3–2.9 (m, 6H), 7.6–8.2 (m, 5H).

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