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4-FURANYL AND 4-THIOPHENYLBUTAN-2-ONE OXIMES

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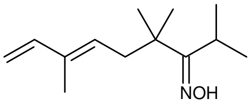
Oximes of 4-(furan-2-yl)butan-2-one, 4-(furan-3-yl)butan-2-one, 4-(5-methylfuran-2-yl)butan-2-one, 4-(thiophen-2-yl)butan-2-one, 4-(5-methylthiophen-2-yl)butan-2-one and 4-(3-methylthiophen-2-yl)butan-2-one have been synthesized. The sensory analysis revealed interesting and complex properties of methyl furan derivative: green, weed-like, similar to herb and flower of nettle. Replacement of oxygen atom by sulfur one in the aromatic ring resulted in creation of smell associated with food.

1. Introduction

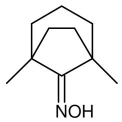
4-Furanyl and 4-thiophenylbutan-2-one can be considered on the one hand as analogues of 6-methylhept-5-en-2-one, an important building block in the synthesis of terpenes, and on the other hand, as analogues of phenyl butanones, known odorants (*e.g.* raspberry ketone). In continuation of our study [1] on synthesis of furanyl analogues of acyclic monoterpenes we could observe that some oximes of the intermediate 4-furanylbutan-2-ones exhibited an interesting scent.

Although, in general, oximes have not been popular fragrances, nevertheless, there are reports on their contribution to the natural scent emanated from flowers being secondary metabolites of aminoacids [2]. Oximes have been previously detected as important contributors of the fragrance of many Flowers [3,4]. The oximes of jasmone and both methyl *trans* and *cis* jasmonates have been identified in the flower of absolute of *Jasmonium auriculatum* Vahl from India [5] and it is believed their contribution to the odour of the absolute is important.

A number of phenyl-aliphatic oximes have been synthesized and characterized olfactorily to exhibit blackcurrant, sage and grape odour notes [6]. Two other ketoximes, 2,4,4,7-tetramethylnona-6,8-diene-3-one oxime (Labienoxime®) and 1,5-dimethylbicycl[3.2.1]octan-8-one oxime (Buccoxime®) with blackcurrant smell have been used for creation of blackcurrant, grapefruit and fantasy notes [7].



2,4,4,7-Tetramethylnona-6,8-diene-3-one oxime
(Labienoxime®)



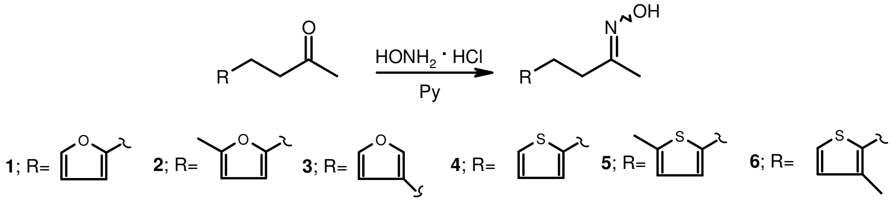
1,5-Dimethylbicyclo[3.2.1]octan-8-one oxime
(Buccoxime®)

It is also worth of notion that oximes are versatile building blocks for construction of heterocycles [8].

The purpose of the work was the synthesis of 6 volatile ketoximes containing a furan or a thiophene core and exhibiting an interesting odour.

2. Results and discussion

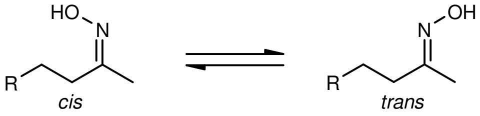
The titled oximes were synthesized from the corresponding furanyl and thiophenylbutan-2-ones (Scheme 1) in standard reaction with hydroxylamine chlorohydride.



Scheme 1. Synthesis of 4-furanyl and 4-thiophenylbutan-2-one oximes

Although the structure of **1** and **5** have been reported earlier [9,10] neither their spectral data are available in the literature, nor their odour properties have been characterized. There is no mention in the literature on the other four oximes.

All the oximes were produced in good yield (88 – 95%) and represented a mixture of *cis/trans* stereoisomers. To identify the stereomers we tried to separate the mixtures by flash chromatography on a silica gel column using hexane/ethyl acetate as an eluent. The successful separation could be accomplish in case of compounds **2** and **5** (isolated GC- pure major component). However, after a few hours at room temperature, the stereoisomers underwent an uncatalysed isomerisation to give a mixture which equilibrated in a couple of days in a ratio of 1: 2.5 (3).



The same phenomenon was observe earlier both in aldoximes and ketoximes even in solid state [11]. Taking into account the above, the structure confirmation and isomer differentiation of the oximes was performed in mixture by ^{1}H and ^{13}C NMR based on the data of methylketoximes ^{1}H NMR detail study[11]. In all ketoximes (**1**-**6**) methyl-protons were shielded by *cis*-hydroxyl group by 13 – 22 Hz indicating to *trans* isomers as the main isomer of the mixture. For example, the shielding effect of hydroxyl group causes a downfield of the Me-protons (δ=1.92) in *trans*-**4** compared to those in *cis*-**4** (δ=1.84). On the other hand, the γ-effect of the hydroxyl causes an upfield shift of the *cis*-Me (δ=13.95) in the *trans*-**4** ^{13}C NMR spectrum in comparison with those in *cis*-isomer (δ=20.13). Similar spectral effects could also be observed for the α-methylene group of the oximes considered. The data clearly point out that the titled oximes represent a thermodynamic mixtures dominated by *trans* (*anti*) isomers.

The sensory analysis revealed interesting and complex properties of methyl furan derivative **2**: green, weed-like, similar to herb and flower of nettle, may be used to induce more naturalness in base notes of perfumes. Incorporating the sulfur, as a third heteroatom in the molecule, creates rather odours associated with food. However, the position of the methyl group in the thiophene ring plays essential role as far as the odour is concerned. It should be noted that the introduction of the methyl substituent to furan core in 5 position brings about an intensive smell in oxime **2**, in comparison with a weak odour of oxime **1**, which may be caused by the increase of lipophilicity of the molecule. Amongst the thiophene derivatives, attention attracts oxime **6** with its meaty smell which is well revealed after a few hours. Odour characteristics of oximes are shown in Table 1.

Table 1

Odour characteristics of oxime **1**-**6**

Oxime	Odour description*
1	Very weak odour
2	Weed-like, herb and flower of nettle, green, a little resembling galbanum, penetrating, tenacious
3	Fruity, prune-like
4	Bread (crust)
5	Leaf of horse-radish
6	Boiled meat (chicken), tenacious

*A test of odour evaluation was done by partly experienced 6 panelists using an EtOH solution (10% v/v) of the sample on a blotter paper

3. Experimental

General

The intermediate furanyl and thiophenyl ketones were prepared from the corresponding furancarboxaldehydes, 2-methylfuran, 2-thiophenecarbox-aldehyde and methylthiophenes purchased from Aldrich, and their spectral data coincided with those reported elsewhere: 4-(furan-2-yl)butan-2-one[12], 4-(furan-3-yl)butan-2-one[13], 4-(5-methylfuran-2-yl)butan-2-one[12], 4-(thiophen-2-yl)butan-2-one[14], 4-(5-methylthiophen-2-yl)butan-2-one[10], 4-(3-methylthiophen-2-yl)butan-2-one[10]. The courses of all reactions, composition products and their purity were checked by means of thin-layer chromatography (TLC) and capillary gas chromatography (GC). The oximes were purified by flash chromatography (silica gel: hexane, ethyl acetate, ether). GC was performed on a Carlo Erba Vega 6000 apparatus equipped with a column Rtx-1 (30 m); temperature program 60-250 ^{o}C (4 ^{o}C/min), N_2 as a carrier gas (0.8 mL/min). GC-MS (mass spectra) were obtained with a Carlo Erba GC coupled to MD 800 Fisons Instruments. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.90 MHz) were recorded in $CDCl_3$ on a Bruker instrument.

General procedure for oxime preparation: 6 Mmol the corresponding furanyl or thiophenyl ketone and 12 mmol hydroxyloxylamine hydrochloride was dissolved in 15 ml of ethanol. Then, 1 ml of pyridine was added and the mixture was refluxed for 2 h. Solvent was removed by evaporation and 20 ml of water was added to the residue. The product was extracted with ethyl acetate (2 x 10 ml) and the organic layer was washed with 5 % hydrochloric acid (10 ml) and water (2 x 10 ml). The extract was dried over $MgSO_4$, filtered and the solvent was removed on a vacuum evaporator. The crude product was flash-chromatographed with the mixture of hexane and ethyl acetate (Hexane:AcOEt; 1:1) on a silica gel column to deliver **1**-**6** oximes in a yield of 88-95 % as *cis/trans* mixtures.

4-(Furan-2-yl)butan-2-one oxime, **1**. ^{1}H NMR (δ): 7.30 (m), 6.28 (m), 6.04 (m), 2.86 (m), 2.68 (m, *cis*), 2.54 (m, *trans*), 1.89 (s, *trans*), 1.82 (s, *cis*). ^{13}C NMR (δ): *trans*-isomer 157.34 (s), 154.55 (s), 141.14 (d), 110.13 (d), 105.22 (d), 34.25 (t), 24.85 (t), 13.55 (q); *trans*-isomer 157.75 (s), 154. 67 (s), 141.14 (s), 110.13 (d), 105.22 (d), 27.35 (t), 23.81 (t), 19.87 (q). MS (m/z):153 (M^+, 72), 136 (96), 124 (58), 108 (27), 95 (35), 94 (18), 81 (100), 67 (23), 53 (56), 42 (55); *cis*-isomer 153 (M^+, 62), 135 (68), 124 (40), 108 (21), 95 (28), 94 (93), (81 (100), 66 (22), 53 (67), 42 (38).

4-(5-Methylfuran-2-yl)butan-2-one oxime, **2**. ^{1}H NMR (δ): 5.88 (m), 5.25 (m), 2.77 (m), 2.68 (m, cis), 2.52 (m, trans), 2.23 (s, *trans*), 1.89 (s, *trans*), 1.82 (s, *cis*); ^{13}C NMR (δ): *trans*-isomer 157.36 (s), 152.64 (s), 150.41 (s), 105.82 (d), 105.78 (d), 34.37 (t), 24.95 (t), 13.53 (q), 13.36 (q); *cis*-isomer 157.77 (s), 152.81 (s), 105.41 (s), 105.81 (d), 105.78 (s), 27.48 (t), 23.83 (t), 19.80 (q), 13.43 (q). MS (m/z): *trans*-isomer 167 (M$^+$, 43), 150 (33), 109 (42), 108 (23), 107 (13), 96 (9), 95 (100), 81 (8), 43 (34), 42 (22); *cis*-isomer 167 (M$^+$, 22), 109 (8), 108 (41), 96 (11), 95 (100), 79 (4), 65 (5), 53 (4), 51 (4), 43 (19).

4-(Furan-3-yl)butan-2-one oxime, **3**. ^{1}H NMR (δ): 7.35 (m), 7.24 (m), 6.28 (m), 2.65 (m), 2.48 (m), 1.90 (s, *trans*), 1.85 (s, *cis*). ^{13}C NMR (δ): *trans*-isomer 157.68 (s), 142.77 (d), 138.39 (d), 123.75 (s), 110.74 (d), 36.13 (t), 21.65 (t), 13. 55 (q); *cis*-isomer 158.08 (s), 142.77 (d), 123.95 (s), 110.74 (d), 28.99 (t), 20.62 (q), 19.90 (t). MS (m/z): *trans*-isomer 153 (M$^+$, 12), 136 (27), 108 (18), 94 (19), 81 (100), 67 (35), 65 (26), 53 (35), 51 (13), 42 (26); *cis*-isomer 153 (M$^+$, 8), 136 (14), 94 (45), 93 (10), 81 (100), 67 (17), 66 (17), 65 (21), 53 (33), 51 (12).

4-(Thiophen-2-yl)butan-2-one, **4**. ^{1}H NMR (δ): 7.13 (m), 6.92 (m), 6.82 (m), 3.07 (m), 2.75 (m, *cis*), 2.59 (m, *trans*), 1.92 (s, *trans*), 1.83 (s, *cis*). ^{13}C NMR (δ): *trans*-isomer 157.47 (s), 143.71 (s), 126.94 (d), 124.63 (d), 123.44 (d), 37.85 (t), 26.91 (t), 13.95 (q); *cis*-isomer 157.79 (s), 143.93 (s), 126.94 (d), 124.63 (d), 123.44 (d), 31.16 (t), 25.67 (t), 20.13 (q). MS (m/z): *trans*-isomer 169 (M$^+$, 8), 152 (4), 136 (5), 111 (41), 110 (18), 97 (100), 58 (10), 53 (6), 45 (17), 42 (23); *cis*-isomer 169 (M$^+$, 10), 111 (21), 110 (48), 98 (9), 97 (100), 77 (7), 58 (9), 53 (8), 45 (15), 42 (16).

4-(5-Methylthiophen-2-yl)butan-2-one, **5**. ^{1}H NMR (δ): 6.57 (m), 2.98 (m), 2.71 (m, *cis*), 2.52 (m, *trans*), 2.43 (s), 1.91 (s, *trans*), 1.85 (s, *cis*). ^{13}C NMR (δ): *trans*-isomer 157.32 (s), 141.26 (s), 137.56 (s), 124.61 (d), 124.08 (d), 37.75 (t), 26.82 (t), 15.16 (q), 13.68 (q); *cis*-isomer 157.70 (s), 141.45 (s), 137.56 (s), 124.61 (d), 124.08 (d), 30.82 (t), 25.67 (t), 20.05 (q), 13.68 (q). MS (m/z): *trans*-isomer 183 (M$^+$, 13), 166 (9), 150 (5), 125 (52), 124 (11), 112 (7), 111 (100), 97 (8), 77 (8), 42 (14); *cis*-isomer 183 (M$^+$, 30), 166 (9), 125 (32), 124 (28), 123 (10), 112 (14), 111 (100), 97 (8), 77 (5), 42 (11).

4-(3-Methylthiophen-2-yl)butan-2-one, **6**. ^{1}H NMR (δ): 6.99 (d, J=5.1 Hz), 6.74 (d, J=5.1 Hz),2.92 (m), 2.62 (m, *cis*), 2.47 (m, *trans*), 2.14 (s, *cis*), 2.13 (s, *trans*), 1.89 (s, *trans*), 1.80 (s, *cis*). ^{13}C NMR (δ): *trans*-isomer 156.99 (s), 136.48 (s), 132.53 (s), 129.57 (d), 120.96 (d), 37.02 (t), 24.68 (t), 13.51 (q), 13.07 (q); *cis*-isomer 157.33 (s), 136.48 (s), 132.53 (s), 129.57 (d), 120.96 (d), 30.66 (t), 23.21 (t), 19.79 (q), 13.06 (q). Ms (m/z): *trans*-isomer 183 (M$^+$, 12), 166 (16), 125 (14), 112 (9), 111 (100), 110 (12), 97 (18), 91 (16), 77 (21), 42 (10); cis-isomer 183 (M$^+$,15), 166 (10), 125 (49), 123 (14), 111 (100), 97 (13), 77 (12), 59 (14), 45 (17), 42 (34).

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OKSYMY 4-FURANYLO I 4-TIOFENYLOBUTAN-2-ONÓW

Streszczenie

W artykule opisano syntezę, charakterystykę spektralną oraz zapachową oksymów 4-(furan-2-ylo)butan-2-onu, 4-(furan-3-ylo)butan-2-onu, 4-(5-metylofuran-2-ylo) butan-2-onu, 4-(tiofen-2-ylo)butan-2-onu, 4-(5-metylotiofen-2-ylo)butan-

2-onu oraz 4-(3-metylotiofen-2-ylo)butan-2-onu. Pochodne metylofuranowe okazały się interesujące pod względem zapachowym. Ich zapach można opisać jako: zielony, podobny do ziela i kwiatu pokrzywy. Zastąpienie atomu tlenu, atomem siarki w pierścieniu aromatycznym skutkowało otrzymaniem związków charakteryzujących się zapachem związanym z żywnością.

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