

ISSN 1561-8331 (Print)  
ISSN 2524-2342 (Online)  
UDC 547.1  
<https://doi.org/10.29235/1561-8331-2019-55-2-171-174>

Поступила в редакцию 17.08.2018  
Received 17.08.2018

P. V. Senin<sup>1</sup>, L. S. Stanishevskii<sup>2</sup>, Y. B. Akayeu<sup>2</sup>

<sup>1</sup>*Atotech-Khemeta Ltd., Moscow, Russian Federation*  
<sup>2</sup>*Belarusian State University, Minsk, Belarus*

## AN IMPROVED METHOD FOR PREPARATION OF HEPTYL (4-TRIFLUOROACETYL)BENZOATE

**Abstract.** A convenient three-step method for synthesis of heptyl (4-trifluoroacetyl)benzoate, an important neutral anion carrier, has been developed. The key step of the method is acylation of toluene by trifluoroacetic anhydride in presence of aluminium chloride at  $-8 - -10$  °C. The procedure gives high overall yield and, unlike the earlier methods, does not include any organometallic reagents, therefore allowing scaling it up to several hundred grams, that makes the target compound much more readily available.

**Keywords:** heptyl (4-trifluoroacetyl)benzoate, neutral anion carrier, trifluoroacetic anhydride, trifluoroacetylation

**For citation.** Senin P. V., Stanishevskii L. S., Akayeu Y. B. An improved method for preparation of heptyl (4-trifluoroacetyl)benzoate. *Vestsi Natsyunal'nai akademii navuk Belarusi. Seryya khimichnykh navuk = Proceedings of the National Academy of Sciences of Belarus. Chemical series*, 2019, vol. 55, no. 2, pp. 171–174. <https://doi.org/10.29235/1561-8331-2019-55-2-171-174>

П. В. Сенин<sup>1</sup>, Л. С. Станишевский<sup>2</sup>, Е. Б. Окаев<sup>2</sup>

<sup>1</sup>*ООО «Атомех-Хемета», Москва, Россия*  
<sup>2</sup>*Белорусский государственный университет, Минск, Беларусь*

## УСОВЕРШЕНСТВОВАННЫЙ МЕТОД ПОЛУЧЕНИЯ ГЕПТИЛОВОГО ЭФИРА 4-ТРИФТОРАЦЕТИЛБЕНЗОЙНОЙ КИСЛОТЫ

**Аннотация.** Разработан удобный трехстадийный метод синтеза гептилового эфира 4-трифторацетилбензойной кислоты, широко применяющегося в потенциометрическом анализе в качестве нейтрального переносчика анионов. Ключевой стадией метода является ацилирование толуола трифторуксусным ангидридом в присутствии хлорида алюминия при  $-8 - -10$  °C. Данная процедура позволяет получить высокий общий выход продукта и, в отличие от описанных в литературе методик, не требует использования металлоорганических реагентов, что позволяет увеличить масштаб синтеза до сотен граммов и сделать целевой продукт значительно более доступным.

**Ключевые слова:** гептиловый эфир 4-трифторацетилбензойной кислоты, нейтральный переносчик анионов, трифторуксусный ангидрид, трифторацетилирование

**Для цитирования.** Сенин, П. В. Усовершенствованный метод получения гептилового эфира 4-трифторацетилбензойной кислоты / П. В. Сенин, Л. С. Станишевский, Е. Б. Окаев // Вест. Нац. акад. наук Беларусі. Сер. хім. навук. – 2019. – Т. 55, № 2. – С. 171–174. <https://doi.org/10.29235/1561-8331-2019-55-2-171-174>

**Introduction.** It is known [1] that double charged anions, being more hydrophilic than single-charged ones, are less likely to be extracted into an organic phase, including the membrane of an ion-selective electrode. To improve their extraction and, therefore, selectivity of their potentiometric determination, usually some neutral ion carrier binding to such anions is introduced into the electrode membrane. For such hydrophilic anions as sulfate, oxalate, acetate and, especially, carbonate, the most popular neutral carriers are trifluoroacetophenone derivatives, notably heptyl (4-trifluoroacetyl)benzoate, or (4-trifluoroacetyl)benzoic acid heptyl ester (TFABAHE), also known as *Carbonate ionophore I* [2].

Despite being commercially available, this compound is not as widely used as it might be, mainly due to its high cost caused by laboriousness of synthesis and necessity for use of organomagnesium or organolithium reagents [3]. The latter factor limits the possibility of large scale preparation and necessitates maintaining water- and air-tight conditions, thus greatly increasing production costs. Therefore, the development of some viable alternative procedure for preparation of TFABAHE is much desired.

The simplest possible way for synthesis of the target compound would be, obviously, through Friedel-Crafts type trifluoroacetylation of a suitable aromatic substrate (such as toluene) using trifluoroacetic anhydride as a reagent, followed by oxidation and esterification. Trifluoroacetic anhydride is known as

a good promoter of aromatic substrate acylation by various carboxylic acids, due to formation of mixed anhydrides as intermediates. However, in those reactions trifluoroacetyl derivatives were never obtained (see, for example, [4]). Several successful trifluoroacetylations of aromatic compounds have been performed up to date. For instance, Ruiz et al [5] introduced trifluoroacetyl group into an aromatic moiety using  $\text{CoCl}_2$  as a catalyst, but in this reaction diphenyl derivatives are formed as by-products, and besides, the method seems to be limited only to alkoxy substituted arenes. A non-catalytic double trifluoroacetylation occurred in [6], but the substrate was a highly reactive tertiary aromatic amine. Similarly, trifluoroacetylation of azulene proceeds without a catalyst [7], due to increased reactivity of its 5-membered ring. The only reference to direct trifluoroacetylation of plain arenes in the literature up to date seems to be in a paper of 1996 [8] where it has been achieved by two-step reaction sequence including preparation of 4-dimethylamino-1-trifluoroacetylpyridinium trifluoroacetate as an acylating agent. Despite reasonably good yields and convenient workup, scaled-up production of 4-trifluoroacetyltoluene and other trifluoroacetylated arenes by this method is not viable from the practical viewpoint, due to considerable amount of waste generated, large excess (more than twofold in total for two steps, taking into account the yield of the first step) of trifluoroacetic anhydride and use of highly flammable and toxic carbon disulfide.

Here we propose the alternative method for trifluoroacetylation of aromatics as a primary step for synthesis of heptyl (4-trifluoroacetyl)benzoate. The whole three step sequence includes treatment of toluene by trifluoroacetic anhydride in presence of aluminium chloride at  $-8 - -10$  °C, followed by dichromate oxidation to a carboxylic acid with its subsequent esterification. As our experiments show, the method is easily scalable to hundred-gram amounts of the target product.

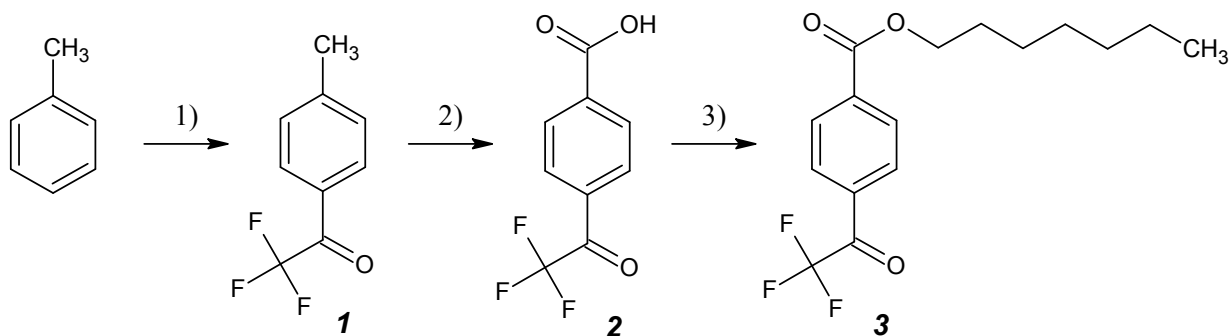
**Results and discussion.** At the first step (Scheme 1), toluene is trifluoroacetylated by the corresponding anhydride in dichloromethane. The reaction proceeds smoothly and in high yield, and the product contains no or almost no *ortho*-isomer admixture, as confirmed by  $^1\text{H}$  NMR spectra. It is very important, however, to maintain the temperature of the reaction mixture no higher than  $-8 - -10$  °C, for which purpose it is best to use a large ice-salt or snow-salt bath. If the temperature raises above this limit (and, especially, if it is allowed to get above 0 °C), considerable poly-acylation and tarring occurs, and the yield drops dramatically. It has been also found that the second important factor affecting the yield is quality of the catalyst; aluminium chloride purchased recently or purified by sublimation just before use, is strongly preferred.

The only significant drawback of this reaction, from the green chemistry viewpoint, is that aluminium chloride is used in excess, not in catalytic amounts, and is irrecoverably lost after the reaction. But, taking into account that it is not a highly toxic waste, the method still appears reasonably good, especially as compared to other synthetic procedures for preparation of the same target compound. It should be also noted that all attempts to decrease the amount of catalyst used without significant yield decrease, have proven unsuccessful.

The conversion of 4-trifluoroacetyl toluene **1** into the corresponding acid has been also improved over the procedure described earlier [3]. First, the use of acetic anhydride in acetic acid was avoided, thus simplifying extraction of the product, acid **2**, from the resulting mixture, and decreasing the amount of organic solvent used. It is essential to note that sodium dichromate, not potassium dichromate, should be used as an oxidizer, because of the risk of potassium hydrogen sulfate crystallization during the synthesis. This can impede stirring and mixing, causing local overheating and possible reaction mixture outburst. However, chromium (VI) oxide works as well as sodium dichromate, although it is more expensive.

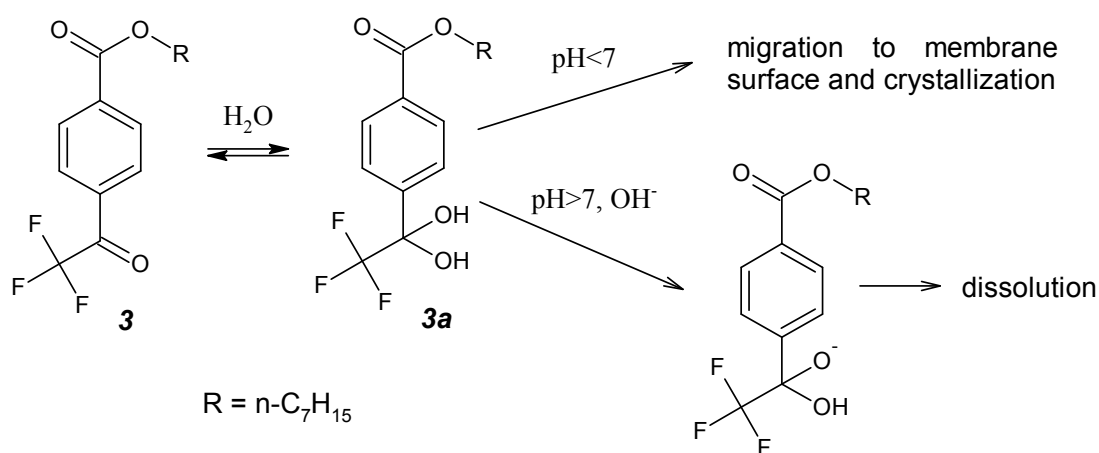
Finally, the third step is a standard esterification reaction. The possible alternative sequence of converting the acid to chloroanhydride, with subsequent ester formation, has proven to give no advantage over direct esterification.

It should be noted that compound **3**, a clear, viscous liquid, easily absorbs water, including atmospheric moisture, producing its hydrated *gem*-diol form **3a**. This process, shown in more detail at Scheme 2, is reversible, but in the water solution the equilibrium is shifted toward hydration. The effect of hydrate formation upon the analytical characteristics of ion-selective electrodes has been earlier discussed in [9].



1)  $(\text{CF}_3\text{CO})_2\text{O}$ ,  $\text{AlCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-10^\circ\text{C}$ ; 2)  $\text{Na}_2\text{Cr}_2\text{O}_7$ ,  $\text{H}_2\text{SO}_4$ ,  $60^\circ\text{C}$ ; 3)  $n\text{-C}_7\text{H}_{15}\text{OH}$ ,  $\text{H}^+$

Scheme 1. Synthesis of 4-trifluoroacetylbenzoic acid heptyl ester (TFABAHE)



Scheme 2. The behavior of compound 3 (TFABAHE) in acidic and basic solutions

**Conclusion.** We report here the improved method for synthesis of heptyl (4-trifluoroacetyl)benzoate (TFABAHE), an important neutral anion carrier. The method does not require any use of organometallic reagents and is easily scalable up to several hundred grams, allowing to produce the target ionophore in much cheaper and cleaner fashion.

**Experimental.** Trifluoroacetic anhydride and aluminium chloride have been purchased from Sigma-Aldrich and had the reagent grade of purity. IR spectra were recorded on Bruker ALPHA spectrometer by attenuated total reflection method (ATR Di) in the range from 4000 to 400  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500.03 MHz) spectra were recorded on a Bruker AVANCE-500 NMR spectrometer.  $\text{CDCl}_3$  was used as a solvent and the residual solvent signals ( $\delta$  7.26 ppm) served as an internal reference standard.

*1-(4-methylphenyl)-2,2,2-trifluoroethanone 1.* Into a 2L three-necked round-bottom flask, equipped with a mechanical stirrer, a thermometer and a dropping funnel, 228 g (1.7 mol) of aluminium chloride and 1200 mL of dichloromethane are placed. The mixture is then cooled to  $-10^\circ\text{C}$  or below by ice-salt or snow-salt mixture. A mixture of toluene (80 mL, 0.753 mol) and dichloromethane (100 mL) is added dropwise, stirred for a short while, and then a mixture of trifluoroacetic anhydride (100 mL, 0.709 mol) and dichloromethane (100 mL) is added dropwise, with vigorous stirring, maintaining the temperature at  $-8^\circ\text{C}$  –  $-10^\circ\text{C}$  or below. Normally the addition is complete within 2h, and the mixture is stirred for 1 additional hour, then poured into 1 kg of broken ice containing 100 ml of concentrated hydrochloric acid. The organic phase is separated, washed with water until neutral, and dried over magnesium sulfate. The solvent is distilled off, the rest is purified by vacuum distillation, collecting the fraction with b.p.  $74\text{--}75^\circ\text{C}$  (15 torr). Yield 125 g (94 %), physical constants correspond to those given in [3]. NMR  $^1\text{H}$ : 2,46 s (3H,  $\text{CH}_3$ ), 7,34 d (2H,  $J = 7,9$  Hz, ArH), 7,97 d (2H,  $J = 7,9$  Hz, ArH).

*4-(Trifluoroacetyl)benzoic acid 2*. To a mixture of 125 mL of water, 300 mL of sulfuric acid and 100 g (0,531 mol) of **1** at 50–60 °C, 214 g (0,718 mol) of sodium dichromate dihydrate is added portion-wise with vigorous stirring, for approximately 1 hour, keeping the temperature below 70°C. The mixture then is stirred at the same temperature for 2 hours, and then heated on a boiling water bath for 15 min, cooled to room temperature and diluted with 500 mL of ice water. The product is extracted with ether (3x200 mL), the combined extracts are dried with magnesium sulfate. The solvent is evaporated in vacuo and the residue is crystallized from toluene, affording compound **2** with m.p. 178–179 °C. Yield 104 g (87 %), physical constants correspond to those given in [3].

*4-(Trifluoroacetyl)benzoic acid heptyl ester 3*. To a round-bottom flask, equipped with a reflux condenser and Dean-Stark receiver, 44 g (0,2 mol) of acid **2**, 42 mL (0,29 mol) of heptanol-1, 200 mL of toluene and 2 g of *p*-toluenesulfonic acid. The mixture is refluxed for approximately 2 hours, until the calculated amount of water is separated. Then the solution is filtered through hydrated silica and toluene is distilled off. The residue is purified by distillation in vacuo (2 torr), collecting a fraction with b.p. 150–155°C and  $n_D^{15}$  1.4720. Yield 65,7 g (88,5 %). IR spectrum,  $\text{cm}^{-1}$ : 2958, 2930, 2859 (CH), 1720 (C = O), 1612, 1588, 1506, 1468 (C = C<sub>arom</sub>). NMR <sup>1</sup>H: 0,84 t (3H, J = 6,8 Hz, CH<sub>3</sub>), 1,36 m (8H, CH<sub>2</sub>), 1,78 m (2H, CH<sub>2</sub>), 4,34 t (2H, J = 7,0 Hz, OCH<sub>2</sub>), 8,09 d (2H, J = 8,5 Hz, ArH), 8,16 d (2H, J = 8,5 Hz, ArH).

The hydrate **3a**, obtained from **3** in presence of water, is a white crystalline compound with no exact melting point (decomposes upon melting). IR spectrum,  $\text{cm}^{-1}$ : 3386, 3323 (broad, OH), 2956, 2937, 2920, 2860, 2848 (CH), 1690 (C = O), 1611, 1579, 1507, 1464 (C = C<sub>arom</sub>). NMR <sup>1</sup>H: 0,84 t (3H, J = 6,8 Hz, CH<sub>3</sub>), 1,37 m (8H, CH<sub>2</sub>), 1,76 m (2H, CH<sub>2</sub>), 4,06 s (2H, OH), 4,29 t (2H, J = 7,0 Hz, OCH<sub>2</sub>), 7,74 d (2H, J = 8,5 Hz, ArH), 7,96 d (2H, J = 8,5 Hz, ArH).

## References

1. Sessler J. L., Gale P. A., Cho W.-S. *Anion Receptor Chemistry*. Cambridge, Royal Society of Chemistry, 2006. 413 p.
2. Behringer C., Lehmann B., Haug J.-P., Seiler K., Morf W. E., Hartman K., Simon W. Anion selectivities of trifluoroacetophenone derivatives as neutral ionophores in solvent-polymeric membranes. *Analytica Chimica Acta.*, 1990, vol. 233, pp. 41–47. [https://doi.org/10.1016/s0003-2670\(00\)83459-5](https://doi.org/10.1016/s0003-2670(00)83459-5)
3. Knunians I. L., Yakobson G. G. (eds.). *Syntheses of organofluorine compounds: monomers and intermediate products*. Moscow, Khimiya Publ., 1977, pp. 251–253 (in Russian).
4. Bourne E. J., Stacey M., Tatlow J. C., Tedder J. M. Studies of trifluoroacetic acid. Part III. The use of trifluoroacetic anhydride in the synthesis of aromatic ketones and sulphones. *Journal of the Chemical Society (Resumed)*, 1951, pp. 718–720. <https://doi.org/10.1039/jr9510000718>
5. Ruiz J., Gilbert L., Astruc D. CoCl<sub>2</sub> catalyzed trifluoroacetylation of aromatics using trifluoroacetic anhydride. *Industrial Chemistry Library. Vol. 8. The Roots of Organic Development*, 1996, pp. 39–47. [https://doi.org/10.1016/s0926-9614\(96\)80008-6](https://doi.org/10.1016/s0926-9614(96)80008-6)
6. Hojo M., Masuda R., Okada E. Nucleophilic nitrogen-nitrogen exchange reaction at aromatic carbon atoms – reaction of N,N-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with various amines. *Tetrahedron Letters*, 1987, vol. 28, no 49, pp. 6199–6200. [https://doi.org/10.1016/s0040-4039\(00\)61845-2](https://doi.org/10.1016/s0040-4039(00)61845-2)
7. Anderson A. G., Anderson R. J. The Reaction of Azulenes with Trifluoro- and Trichloroacetic Anhydride. *Journal of Organic Chemistry*, 1962, vol. 27, no. 10, pp. 3578–3581. <https://doi.org/10.1021/jo01057a044>
8. Simchen G., Schmidt A. Eine einfache Methode zur Darstellung von Aryl-trifluormethylketonen. *Synthesis*, 1996, no. 9, pp. 1093–1094. <https://doi.org/10.1055/s-1996-4444>
9. Matveichuk Y., Akayeu Y., Rakhman'ko E. Hydration of *p*-trifluoroacetyl benzoic acid heptyl ester: how it affects analytical characteristics of sulfate selective electrodes based on higher quaternary ammonium salts. *Chemical Papers*, 2018, vol. 72, no. 2, pp. 509–514. <https://doi.org/10.1007/s11696-017-0294-5>

## Информация об авторах

Сенин Павел Владимирович – инженер по продажам, ООО «Атотех-Хемета» (Волоколамское шоссе 73, оф. 623, 125424, Москва, Российская Федерация). E-mail: [senin\\_pv@mail.ru](mailto:senin_pv@mail.ru)

Станишевский Леонид Станиславович – д-р хим. наук, профессор, Белорусский государственный университет.

Окаев Евгений Борисович – канд. хим. наук, доцент, вед. науч. сотрудник, Белорусский государственный университет (ул. Ленинградская, 14, 220030, Минск, Республика Беларусь). E-mail: [akayeu@bsu.by](mailto:akayeu@bsu.by)

## Information about the authors

Pavel V. Senin – Sales Engineer, Atotech-Khemeta Ltd. (73, Volokolamskoe Highway, office 623, 125424, Moscow, Russian Federation). E-mail: [senin\\_pv@mail.ru](mailto:senin_pv@mail.ru)

Leonid S. Stanishevskii – D. Sc. (Chemistry), Professor, Belarusian State University.

Yauhen B. Akayeu – Ph. D. (Chemistry), Associate Professor, Leading Researcher, Belarusian State University (14, Leningradskaya Str., 220030, Minsk, Republic of Belarus). E-mail: [akayeu@bsu.by](mailto:akayeu@bsu.by)