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GEORGE A. OLAH DOCTORAL SCHOOL

Synthesis of trifluoroethyl phosphonates and investigation of their effect on the selectivity of Horner-Wadsworth-Emmons reaction

SUMMARY OF PHD THESIS

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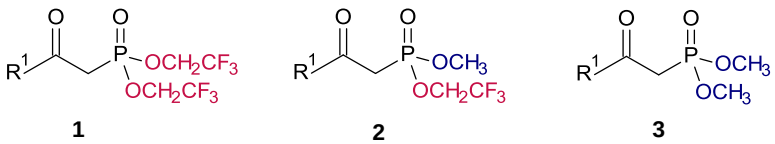
1. INTRODUCTION

The Prostaglandin Business Unit of Chinoin is amongst the world-leading pharmaceutical companies for the synthesis of prostaglandin (PG) APIs (active pharmaceutical ingredients). One of the key steps in the synthesis of PGs is the preparation of side-chain double bonds by means of Wittig and/or Horner-Wadsworth-Emmons (HWE) reactions. However, these reactions are never completely selective, which involves appearance of the undesirable isomer of the favourable biological effect bearing compound in the product. Strict regulatory requirements apply to the impurity profile of the end products, therefore, all the possible isomeric impurities must be identified and measured by analytical methods in the products.

Synthesizing PGs is a complicated, multi-step task, where preparation of the isomeric impurities can be more difficult than that of the products, the generally natural compounds. The aim of our research was to be able to synthesize PGs and PG analogues bearing *E* or *Z* double bonds in their side-chains on-demand by modifying reagents and reaction parameters of HWE reaction in the simplest way possible. The simpler our influence on the stereoselectivity of the reaction, the more efficient and economical the synthesis of the APIs to be sold and the required isomers may be. To investigate the *E*- and *Z*-selective HWE reaction, we chose to examine model compounds similar to PG intermediates.

It is well known that the use of dimethyl phosphonates leads to olefins with excellent *E*-selectivity in HWE reaction, while - according to literature data - bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates cause high *Z*-selectivity. Through these findings we intended to further investigate the selectivity of HWE reaction. During our work, we reacted dimethyl (**3**), 2,2,2-trifluoroethyl methyl (**2**) and bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates (**1**) with different aldehydes and determined the isomeric ratio of the formed double bond bearing compounds.



1 **2** **3**

Figure 1: Phosphonates applied in HWE reaction[1]

[1] Compound numbers in the Summary refer to the compound numbers used in the PhD thesis.

2. LITERATURE REVIEW

2.1. Horner-Wadsworth-Emmons (HWE) reaction[2]

HWE reaction (Figure 2.) is a modified Wittig reaction. Lithium, sodium or potassium salt of a *β*-keto- or *α*-(alkoxycarbonyl)phosphonic acid dialkyl ester is applied as the phosphorous compound, which is reacted with an aldehyde or keton to produce *α,β*-unsaturated ketons or esters with high *E*-selectivity.

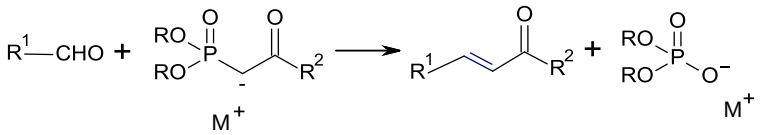


Figure 2: General scheme of HWE reaction

2.1.1. Still-Gennari reaction[3] and its modification by Jin[4]

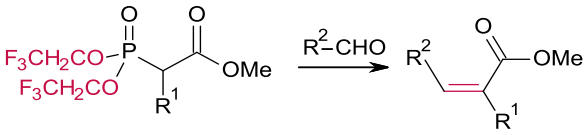


Figure 3: Z-selective HWE reaction with Still-Gennari reagent

Still and Gennari discovered a practical method to prepare di- and trisubstituated unsaturated esters, i.e. acrylic- and metacrylic esters with high *Z*-selectivity in HWE reaction (Figure 3.). Different aromatic, aliphatic and unsaturated aliphatic aldehydes were reacted with bis(2,2,2-trifluoroethyl) phosphonoesters and the selectivity influencing role of bases were investigated. The KHMDS/18-crown-6 system provided best selectivity, namely, when deprotonation of phosphonate was achieved by a strongly dissociated base system.

Jin further developed Still and Gennari's method to synthesize *Z-α,β*-unsaturated ketones, and reacted bis(2,2,2-trifluoroethyl) 2-oxopropylphosphonate reagent with several aldehydes. He achieved 100% selectivity with aromatic aldehydes, while in the case of aliphatic aldehydes, selectivity was significantly lower (*Z*/*E* = 3-10:1).

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[2] Bruckner, R.; Harmata, M. (ed.) *Organic mechanisms – Reactions, Stereochemistry and Synthesis*, Springer-Verlag: Berlin Heidelberg, **2010**, pg. 457-467.
[3] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-8.
[4] Yu, W.; Su, M.; Jin, Zh. *Tetrahedron Lett.* **1999**, *40*, 6725-8.

2.2. Preparation of bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates (1)

Bis(2,2,2-trifluoroethyl) methylphosphonate and phosphonoesters have been prepared by multi-step transformation from dialkyl phosphonates.[3,5,6,7,8] The first step of the synthesis is chlorination of the starting phosphonate, followed by the reaction of phosphonic dichloride with trifluoroethanol. However, preparation of bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates by this route hasn't been published yet.

Most of the time bis(2,2,2-trifluoroethyl) phosphonoesters, i.e. Still-Gennari-type phosphonates are synthesized by acylation. Savignac et al[8] elaborated this process, where the starting bis(2,2,2-trifluoroethyl) methyl- or ethylphosphonate was deprotonated by LiHMDS, followed by acylation of the phosphonate anion with ethyl chloroformate.

In order to prepare bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates Jin modified the method of Savignac.[3] This meant that the solution of phosphonate and ester was not added dropwise to the base but first, bis(2,2,2-trifluoroethyl) methylphosphonate was added to the pre-cooled solution of the base, then the appropriate acyl chloride was added to the deprotonated phosphonate, instead of an ester (Figure 4.). The reaction mixture was cooled to -98°C, because the lithiated phosphonate formed during deprotonation was unstable even at -78°C.

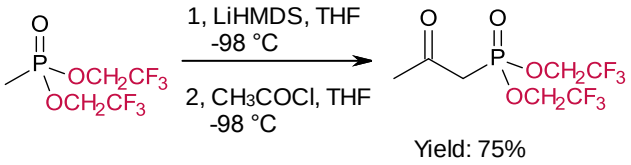

Figure 4: Jin's method for the synthesis of bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates

Within the literature only some examples exist for the preparation of bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates. Jin's method was applied in every case.

2.3. Preparation of 2,2,2-trifluoroethyl methyl 2-oxoalkylphosphonates (2)

The effect of mixed, *Z*- and *E*-selective properties (methyl and 2,2,2-trifluoroethyl group) bearing phosphonates hasn't been investigated in classic HWE reaction before, and the mixed 2-oxoalkylphosphonates are unknown compounds.

[5] Gutch, P. K.; Singh, R.; Acharya, J. *J. Appl. Polym. Sci.* **2011**, *121*, 2250-6.
[6] Bechtold, W. E.; Dahl, A. R. *J. Labelled Compd. Rad.* **1985**, *22*, 1181-6.
[7] Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Org. Synth.* **1996**, *73*, 152-8.
[8] Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Synthetic Commun.* **1991**, *21*, 2391-6.

2.4. Environmentally friendly preparation of bis(2,2,2-trifluoroethyl) methylphosphonate (7)

We set out the aim of elaborating a process by which bis(2,2,2-trifluoroethyl) methylphosphonate - a common starting material of phosphonates used for *Z*-selective HWE reaction - can be prepared by means of cheap reagents in an environmentally friendly way. According to literature findings, the above phosphonate is prepared in two steps through phosphonic dichloride.[5-8] The chlorination step cannot be considered as environmentally friendly and for this, we intended to omit it, i.e. to prepare the molecule by direct esterification of the starting dimethyl methylphosphonate. According to our knowledge, direct esterification with trifluoroethanol through conventional chemical methods cannot be executed.

The use of microwave reactors and flow reactors broadens as these devices are acknowledged to be environmentally friendly and safe. Through microwave activation the efficiency of chemical transformations can be increased, reactions can be made faster and more selective, and it is possible to perform reactions that cannot be realised under conventional reaction conditions. The great advantages of flow reactors are the simultaneously small reaction volumes of chemicals in the reactor and temperature control (hence the safe working conditions), controllable residence time, effective mixing, quick optimizations and higher yield and/or selectivity of reactions. Due to the easily manageable working conditions at high pressure, temperature can be increased above the boiling point of the applied solvent, again allowing reactions to be performed that couldn't be realised under conventional conditions.

3. EXPERIMENTAL AND COMPUTATIONAL METHODS

The progress of the reactions and the purity of the compounds was determined by gas chromatography on a Shimadzu GCMS-QP2010 Ultra and an Agilent 6890N (GC-FID) equipment.

The structure of products were identified by ^{1}H, ^{13}C and ^{31}P NMR spectra on a Bruker AvanceIII equipment at 500,15 MHz, 125,8 MHz and 202,5 MHz with tetramethylsilane (TMS) as internal standard.

The HRMS analysis was performed on an Acquity UPLC/Micromass, Q-TOF Premier spectrometer.

Microwave (MW) reactions were carried out in a CEM Discover-Explorer MW reactor.

We used ThalesNano's Phoenix flow reactor for the continuous flow experiments.

Computations were carried out with the Gaussian09 program package (G09) at B3LYP/6-31G(d,p) level of theory.

4. RESULTS

In order to investigate the factors affecting selectivity of the Horner-Wadsworth-Emmons reaction, we first had to synthesize the phosphonates chosen as model compounds (Figure 5.), since only dimethyl 2-oxopropylphosphonate (**3a**) may be obtained commercially.

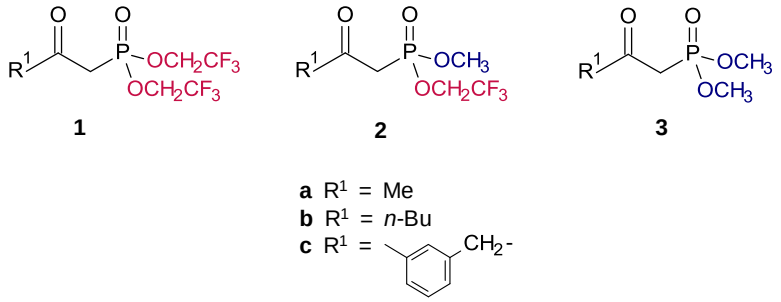

Figure 5: Synthesis of model phosphonates

4.1. Preparation of bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates (1)

4.1.1. By multi-step transformation of dimethyl 2-oxoalkylphosphonates (3)

Dimethyl 2-oxoalkylphosphonates (**3**) were prepared by known method of acylation of dimethyl methylphosphonate. **3** phosphonates were successfully transformed into **1** phosphonates in three steps. The first step is a silylation reaction under neat conditions and at room temperature that took place quantitatively. Next comes a chlorination step providing the appropriate phosphonic dichloride with oxalyl chloride in the presence of a catalytic amount of DMF. The solvent is dichloromethane, still at room temperature and phosphonic dichloride formed quantitatively. The final step is the esterification reaction with trifluoroethanol in pyridine (solvent and base) at 50°C with 4-dimethylaminopyridine (DMAP) catalyst, with

approximately 50% yield after chromatographic purification (Figure 6.) This means that the reaction sequence provided all three **1** phosphonates with circa 50% yield after purification.

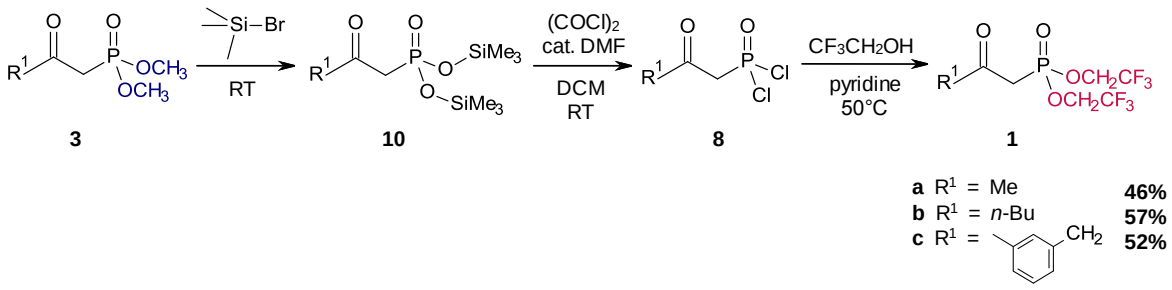

*Figure 6: Preparation of bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates (**1**) in three steps*

This method is favourable from a practical point of view since *Z*-selectivity providing **1** bis(2,2,2-trifluoroethyl) phosphonates can be prepared by simply transforming the ester functional group of the *E*-selectivity providing **3** dimethyl phosphonates. In addition, the synthesis applies mild reaction conditions, doesn't require extreme high temperature or pressure and contains easily scalable steps.[I]

4.1.2. By acylation reaction of bis(2,2,2-trifluoroethyl) methylphosphonate (7)

One of our aims was to optimize the acylation method used widely according to literature findings, since we had issues preparing **1** phosphonates with appropriate yield via this type of reaction. Optimization reactions were carried out on bis(2,2,2-trifluoroethyl) 2-oxohexylphosphonate (**1b**). We investigated the impact of temperature, base, equivalency, carboxylic acid derivatives, type of addition and temperature of reagents but no significant improvement could have been achieved. However, altering the means of addition and replacing the acyl compound did result in higher yield. Conducting the reaction at -90°C with LiHMDS proved to be the most suitable (Figure 7.).

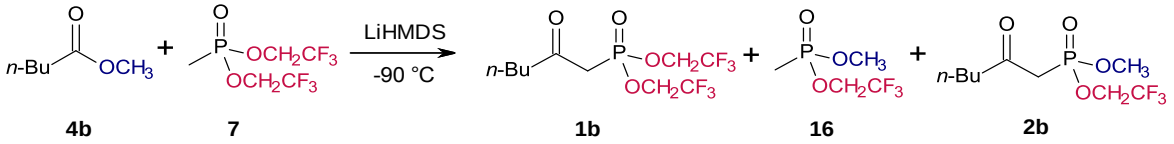

*Figure 7: Optimized acylation reaction for the preparation of **1b** phosphonate*

By applying the optimized reaction conditions, we synthesized a number of new bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates (**1**) in pure form after chromatographic purification.

This way the overall reaction time became shorter and requires milder reaction conditions than the literature method, resulting in a cleaner reaction and so allowing easier purification.[III]

The main impurities (**16** and **2b**) formed during the acylation reaction were isolated and identified, the probability of formation was supported by quantum chemical calculations and these calculations were confirmed by independent preparative experiments. We ascertained that 2,2,2-trifluoroethyl methyl methylphosphonate (**16**) is formed from the starting **7** bis(2,2,2-trifluoroethyl) phosphonate and LiOMe that is formed *in situ* during the reaction, while 2,2,2-trifluoroethyl methyl 2-oxohexylphosphonate (**2b**) can be formed only from **16** side-product by acylation and not from **1b** phosphonate. During the acylation reaction two other impurities were formed, two dimer-type compounds: a Claisen-type side-product from the **4b** ester and the bis(2,2,2-trifluoroethyl) ((2,2,2-trifluoroetoxy(methyl)phosphinoyl)methyl)phosphonate (**19**) from the **7** starting phosphonate.

Additional quantum chemical computations confirmed the difference between reactivity of the applied carboxylic esters during the acylation reaction.

4.2. Preparation of 2,2,2-trifluoroethyl methyl 2-oxoalkylphosphonates (2)

Preparation of mixed phosphonates was based on the multi-step transformation of dimethyl phosphonates into bis(2,2,2-trifluoroethyl) phosphonates. First, dimethyl 2-oxoalkylphosphonates (**3**) were converted to phosphonic acid monoester (**24**) by basic hydrolysis with aqueous solution of KOH at 50°C. The first step yielded the half acid-half esters with 70-95% because of their high water-solubility. The next step was esterification with trifluoroethanol. This went well with the Steglich-type reaction, which included reaction of **24** phosphonates with *N,N'*-dicyclohexyl- (DCC) and *N,N'*-diisopropylcarbodiimide (DIC) in the presence of DMAP as catalyst. **2** phosphonates were prepared with cca. 40% yield (Figure 8.).[II]

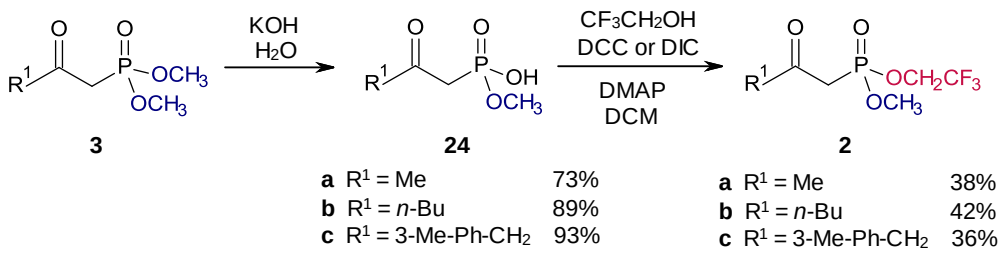

*Figure 8: Synthesis of 2,2,2-trifluoroethyl methyl 2-oxoalkylphosphonates (**2**)*

4.3. Environmentally friendly preparation of bis(2,2,2-trifluoroethyl) methylphosphonate (7)

According to the literature, bis(2,2,2-trifluoroethyl) methylphosphonate (**7**) cannot be prepared conventionally by direct esterification from the analogous dimethyl methylphosphonate (**6**). However, by application of flow chemistry at high temperature and high pressure we managed to perform direct esterification in an environmentally friendly way since only the starting dimethyl phosphonate and trifluoroethanol (required for the transesterification) were used. Optimization reactions were carried out by means of ThalesNano's Phoenix flow reactor and the effect of temperature, pressure and catalyst (0,05 eq. sulphuric acid) was investigated. It has been ascertained that this reaction requires extreme reaction conditions to take place and there is no need for a catalyst for a proper conversion. Conversion was set above 80% at 450°C and 200 bars, so we performed a scale-up using these parameters. Transformation was put through with 100 equivalents of trifluoroethanol (0,016 g/ml alcoholic solution), 0,4 ml/min flow rate and 20 minutes residence time. By this method, cca. 370 ml reaction mixture was collected, the excess trifluoroethanol was recovered, then bis(2,2,2-trifluoroethyl) methylphosphonate (**7**) was purified by column chromatography to cca. 55% yield.

4.4. Horner-Wadsworth-Emmons reactions

The pre-prepared 2-oxopropyl, 2-oxohexyl and 3-(3-methylphenyl)-2-oxopropyl chain bearing bis(2,2,2-trifluoroethyl) (**1**), 2,2,2-trifluoroethyl methyl (**2**) and dimethyl phosphonates (**3**) were used to investigate *E*- and *Z*-selective HWE reactions. Phosphonates were reacted with three aldehydes: benzaldehyde (**31**) and the important, frequently applied reagents in prostaglandin chemistry: tetrahydropyranyl- (THP) (**32**) and 4-phenylbenzoyl- (PPB) Corey aldehyde (**33**). Two reaction conditions were used to study reactions. The so-called „*cis*" protocol became the method introduced by Still and Gennari (KHMDS, 18-crown-6, -78°C, THF), with which best *Z*-selectivity can be achieved, while „*trans*" protocol represents our own, generally applied method (KOH, 0°C, toluene) that is appropriate for *E*-selective double bond formation.

We ascertained that the alkoxy group attached to P-atom, i.e. the ester function of the phosphonate has the greatest effect on the stereoselectivity of HWE reaction. However, to achieve high *Z*-selectivity, it is essential to use both the appropriate bis(2,2,2-trifluoroethyl) phosphonate (**1**) and the reaction conditions of „*cis*" protocol (-78°C, KHMDS, 18-crown-6).

Applying even mixed phosphonates (**2**), *Z*-selectivity decreases approximately to half of this ratio, which means that a mix of *Z* and *E* products is formed in the reaction. Using dimethyl phosphonates (**3**), only a tiny amount of *Z* product is formed in the reaction mixture, even with „*cis*" protocol.

The bulkiness and electronical properties of the applied aldehyde has a large impact on the stereochemistry of the forming double bond. The almost 100% *Z*-selectivity achieved by benzaldehyde with „*cis*" protocol was decreased to cca. 60-70% in the reaction of PPB- and THP-Corey aldehyde and **1** phosphonates. In contrast, R^1 alkyl chain of phosphonates has a slight impact on the *Z*/*E* ratio. However, in certain cases, a 20% difference may be observed.[V]

5. THESES

1. We developed a multi-step transformation reaction of dimethyl 2-oxoalkylphosphonates to bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates for the first time. The generally applicable synthesis takes place through bis(trimethylsilyl) phosphonate and phosphonic dichloride and contains mild reaction conditions and scalable steps. [**I**]
2. A new process was elaborated for the preparation of bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates by acylation. This new method resulted in a shorter reaction time and milder reaction conditions than the previously well-known process documented in the literature. [**III**]
3. We investigated and demonstrated by experiments and computations the circumstances of formation of the side-products formed during the acylation reaction of bis(2,2,2-trifluoroethyl) methylphosphonate. Furthermore, quantum chemical computations confirmed the observed difference between the reactivity of certain carboxylic esters during reaction.
4. We were the first to prepare 2,2,2-trifluoroethyl methyl 2-oxoalkylphosphonates and investigated their effect on the stereoselectivity of HWE reaction. We ascertained that in case of the application of proper reaction conditions and reagents cca. 65% *Z*-selectivity may be achieved with these mixed phosphonates. [**II**, **IV**, **V**]
5. According to literature findings, we successfully pioneered the execution of direct esterification of dimethyl methylphosphonate with trifluoroethanol to bis(2,2,2-

trifluoroethyl) methylphosphonate without added reagents or catalysts. The reaction took place in a flow reactor in an environmentally friendly way.

6. APPLICATION OF SCIENTIFIC RESULTS

By means of our two newly-elaborated synthetic procedures bis(2,2,2-trifluoroethyl) 2-oxoalkylphosphonates can be prepared, which are key reagents for the *Z*-selective preparation of *α,β*-unsaturated ketons in the Horner-Wadsworth-Emmons reaction. The processes apply diverse starting materials, reagents and conditions, and, because of this, the method of phosphonate formation is optional. With mixed, 2,2,2-trifluoroethyl methyl 2-oxoalkylphosphonates, that are easy to prepare, *Z*-selectivity may be increased above 50% when applying the appropriate reaction conditions and reagents. This makes them convenient reagents to synthesize *Z*- and *E*-*α,β*-unsaturated ketons together through only one reaction.

The new synthetic procedures may bring significant savings in costs and time primarily in the design of industrial synthesis of prostaglandins and in the preparation of isomeric impurities required for the certification of products. In addition, they may be usefully applied in the field of plant-health industry, as well, for the preparation of such molecules that contain *Z/E* double bonds.

7. PUBLICATIONS

7.1. Full scientific publications related to the PhD Thesis

I. Molnár, K.; Takács, L.; Kádár, M.; Kardos, Zs.; Faigl, F.: A Practical Route for the Preparation of Bis(2,2,2-trifluoroethyl) 2-Oxoalkylphosphonates; *Synthesis* **2015**, *47*, 1085-90. [IF: **2,689**]

II. Molnár, K.; Behra, J.; Takács, L.; Kádár, M.; Kardos, Zs.; Faigl, F.: A Convenient Procedure For the Synthesis of 2,2,2-Trifluoroethyl Methyl 2-Oxoalkylphosphonates; *Phosphorus, Sulfur Silicon Relat. Elem.* **2015**, *190*, 677-80. [IF: **0,561**]

III. Molnár, K.; Takács, L.; Kádár, M.; Faigl, F.; Kardos, Zs.: A Practical Process for the Preparation of Bis(2,2,2-trifluoroethyl) 2-Oxoalkylphosphonates by Acylation with Carboxylic Esters; *Tetrahedron Lett.* **2015**, *56*, 4877-9. [IF: **2,379**]

IV. Molnár, K.; Takács, L.; Kardos, Zs.; Faigl, F.: Út a prosztaglandin kettős kötések tetszőleges geometriájú kialakítása felé; *IV. Interdiszciplináris Doktorandusz Konferencia*, Pécs, **2015**.05.14-15. Conference booklet (ISBN 978-963-642-830-3), pp. 511-523. [IF: -]

V. Molnár, K.; Takács, L.; Kádár, M.; Faigl, F.; Kardos, Zs.: *Z*- and *E*-selective Horner-Wadsworth-Emmons (HWE) reactions; *Synth. Commun.* – submitted on February 28. 2017.

7.2. Oral presentations

I. Molnár, K.; Behra, J.; Takács, L.; Kardos, Zs.; Faigl, F.: Stabilizált foszfonátok Wittig-reakciói – avagy cisz vagy transz kettős kötést parancsol, uram?; *XXXVI. Kémiai Előadói Napok*, Szeged, **2013**.10.28-30.

II. Molnár, K.; Behra, J.; Takács, L.; Kardos, Zs.; Faigl, F.: HWE reactions of Stabilized Phosphonates: Investigating the Scope and Limitations of the Still-Gennari Method; *International Conference on Phosphorous Chemistry (ICPC)*, Dublin, Ireland, **2014**.06.28.-07.02.

III. Molnár, K.; Takács, L.; Kardos, Zs.; Faigl, F.: Új módszerek trifluoretil-foszfonátok előállítására, és cisz-transz szelektivitásuk vizsgálata HWE-reakciókban; *Oláh György Doktori Iskola Konferenciája*, Budapest, **2015**.02.05.

IV. Molnár, K.; Takács, L.; Kardos, Zs.; Faigl, F.: Út a prosztaglandin kettős kötések tetszőleges geometriájú kialakítása felé; *IV. Interdiszciplináris Doktorandusz Konferencia*, Pécs, **2015.**05.14.-15.

V. Molnár, K.; Takács, L.; Kardos, Zs.; Faigl, F.: Trifluoretil 2-oxoalkilfoszfonátok előállítása új módszerekkel, és hatásuk vizsgálata a Horner-Wadsworth-Emmons reakciókban; *MKE 2. Nemzeti Konferencia*, Hajdúszoboszló, **2015**.08.31.-09.02.

7.3. Poster presentations

I. Molnár, K.; Behra, J.; Takács, L.; Kardos, Zs.; Faigl, F.: Stabilizált foszfonátok HWE-reakciói – A Still-Gennari protokoll kiterjeszthetőségének vizsgálata; *Oláh György Doktori Iskola Konferenciája*, Budapest, **2014**.02.06.

II. Molnár, K.; Behra, J.; Takács, L.; Kardos, Zs.; Faigl, F.: Novel Methods for the Preparation of Trifluoroethyl-phosphonates and their Use in HWE reactions;

European Association for Chemical and Molecular Sciences Chemistry Congress (EuCheMS), Istanbul, Turkey, **2014**.08.31.-09.04.

III. Molnár, K.; Takács, L.; Kardos, Zs.; Faigl, F.: Route to the Controlled Formation of Prostaglandin Double Bonds; *SCS Fall Meeting*, Lausanne, Switzerland, **2015**.09.04.