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A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901655

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901655

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10.1002/ejoc.201901655

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Fast-Synthesis of α-phosphonyloxy ketones as Drug Scaffolds in a Capillary Microreactor

Bandaru T. Ramanjaneyulu,[a] Shinde Vidyacharan,[a] Se Jun Yim,[a] and Dong-Pyo Kim*[a]

Abstract: A simple and room temperature approach for the fast single-step synthesis of α-phosphonyloxy ketone, a drug scaffold, has been developed which involves a highly reactive species *i.e.,* 1,2-dicarbonyls that combine readily with trialkyl phosphites and formic acids in batch as well as continuous-flow. The present approach reduced the synthesis time from hours to minutes in batch, which was further lowered to a few seconds precisely controlled by single capillary microfluidics. A wide range of 1,2-dicarbonyl derivatives were smoothly transformed to their corresponding α-phosphonyloxy ketones in moderate to good yields (50-82%) in continuous-flow with the flow rate of 3 ml/min (t^R = ~4 s). Further, the α-phosphonyloxy ketones produced can be utilized in batch process to form benzoin, oxazole core, and *α,α'*-diarylated carbonyl compounds in 82%, 50%, and 54% yields, respectively, which are alternative key precursors/scaffolds of natural products and active pharmaceutical ingredients (APIs).

Continuous-flow microreactors have recently attracted much attention as an important technique for synthesizing organic molecules including drug intermediates/molecules in a very short time under mild reaction conditions.[1-4] A high surface area to volume ratio in the microfluidic system promotes mass and heat transfer, leading to selectivity and conversion much superior to the levels obtainable by conventional batch processes.[2-4] Owing to their many complex issues such as inefficient mixing, non-uniformity in heat, and safety in the scale-up of batch process, in recently, flow approach is more attractive and reliable in both academia and industry.[1,2] Furthermore, high throughput production can be achieved by simply increasing reaction volume with larger dimension of channel, or/and by numbering up microreactor units in parallel.[5,6] In light of the push for continuous manufacturing of pharmaceutical products[7,8] microreactor can be an attractive alternative to the conventional batch process for many of the pharmaceutical products whose world-wide consumption is of the order of tons a year. Therefore, simple and fast continuous-flow methodologies are highly desirable to operate at high flow rate, enabling to satisfy the changing needs of pharmaceutical markets in a safe and environmentally benign, cost-effective manner.

On the other hand, the organophosphate chemistry by itself is an interesting area of organic chemistry as well as life science in living organism such as DNA, RNA, ATP and cell membranes.[9] Moreover, various methodologies also reported for the synthesis of various organophosphates with applications ranging from agrochemicals to biologically active phosphate medicines.[10-12] Among them, α-phosphonyloxy ketones serve as key motifs[10] in the synthesis of oligonucleotide, sugar analogues, phospholipids and also versatile key intermediates in natural products.

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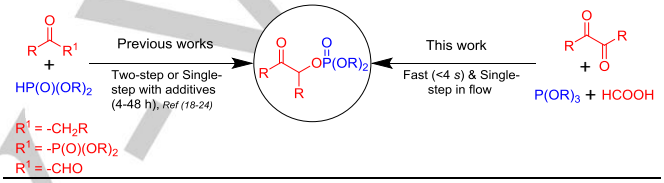
Not surprisingly, α-phosphonyloxy ketones are also of great interest to serve as core structures of synthetic drugs such as prednisolone[13] and oxaprozine drug[14] derived from benzoin, and bupropion drug[15] derived from corresponding acyloin. However, selective synthetic routes to α-phosphonyloxy ketones are less prevalent over numerous reports on the synthesis of various organophosphates.[16,17] Single-step or one-pot synthesis for α-phosphonyloxy ketones is more attractive than two-step approaches including extra synthetic step of intermediates (Scheme 1).[18-21] The routes reported in the literature for the synthesis of α-phosphonyloxy ketones require a long time *up to* 48 h at room temperature (RT),[18-20] 4 h to 48 h even at high temperature (*up to* 80 °C),[21-24] and also produce massive by-products[18-20,22,24] (Scheme 1).



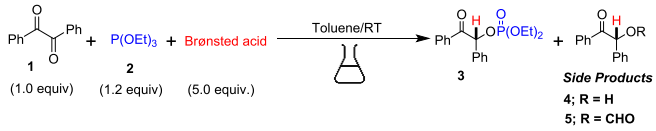
Scheme 1. Comparative approaches for the synthesis of α-phosphonyloxy ketones between the reported work and our work.

Here, we developed a new method which involves a highly reactive species *i.e.,* 1,2-dicarbonyls that combine readily with trialkyl phosphites and formic acids to produce the α-phosphonyloxy ketones, precisely controlled by microfluidics. The present approach reduced the synthesis time from hours to minutes in batch, which was further lowered to a few seconds at room temperature precisely controlled by microfluidics. Importantly, using this approach, α-phosphonyloxy ketones could be easily access at room temperature in fast (residence time 3.93 s), safe, environmentally benign and compact compared to conventional batch process. Moreover, most of the reported methods[18-24] involves various phosphites as starting materials known as potentially neurotoxic reagents for the synthesis of α-phosphonyloxy ketones.

Our initial optimization studies were carried out in batch using benzil **1** and triethyl phosphite **2** as model substrates under various reaction conditions (Table 1). The reaction in the absence of acid using toluene as a solvent at room temperature didn't give expected product *i.e.*, α-phosphonyloxy ketone **3** (entry 1). However, in the presence of H_2O the expected product **3** was obtained in 32% yield for 12 h along with the formation of side product benzoin **4** in 10% yield. Encouraging these results, further optimization experiments were performed by screening different acids (entries 3–7). The yields of the product **3** were improved to 54% yield with HCl acid (entry 3), 44% yield with PTSA acid (entry 6), 67% yield with AcOH acid (entry 7) after long time for 12 h. Whereas product **3** was not obtained with strong acids such as H_2SO_4 & TfOH acids (entries 4 & 5) that could be due to decreasing the reactivity of α-dicarbonyl compounds in the presence of strong acids. Interestingly, when the reaction was executed with HCOOH (**6**) as an acid source in toluene solvent at room temperature, the desired product **3** was isolated in 67% yield in very short time (5 min) (entry 8) along

with side products benzoin **4** & the oxy-formylated products (**5**) in 5% & 21% yields, respectively. The chosen high reactive starting material (**1**) with triethyl phosphite in the presence of an appropriate strong acid, *i.e.,* HCOOH, accelerated the reaction to dramatically decrease the reaction time under preferable conditions (direct, oxidant-free, RT). Note that the lower concentration of benzil **1** from 0.2 M to 0.1 M took longer time (10 min) to reach similar yields of products (entry 9).

Table 1. Synthesis of *α*-phosphonyloxy ketone from *α*-dicabonyl compound and triethyl phosphite in batch[a]

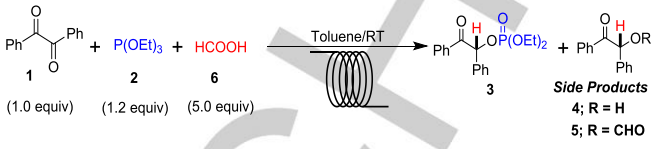


Entry	Acid source	Time	Yield 3:4:5 (%)[b]
1	--	1 h	0:0:0
2	H_2O	12 h	32:10:0
3	HCl	12 h	54:12:0
4	H_2SO_4	12 h	NR
5	TfOH	12 h	NR
6	PTSA	12 h	44:0:0
7[c]	AcOH	12 h	67:<5:10
8	**HCOOH (6)**	**5 min**	**67:5:21**
9[d]	HCOOH	10 min	67:5:23

[a] Reaction conditions: 0.2 M of **1** (1 mmol scale)**,** 1.2 equiv. of **2** with respect to **1**, 5.0 equiv. of acid were found to be optimal in N_2 atmosphere. NR; No reaction. RT; Room temperature = 23–26 °C. TfOH = Triflic acid, PTSA = *p*-Toluene sulfonic acid. [b] Isolated yields. [c] In this case, the corresponding oxy-acylated side product (10% yield) was formed instead of oxy-formylated product (**5**). [d] 0.1 M of 1.

With the synthesis time reduced to several minutes (5 min) from several hours (4 hrs),[24] the developed organophosphate chemistry was directly applied to continuous-flow single capillary reactor (Table 2). The three reagents in toluene were individually injected at different concentrations, solvents and flow rates into a simple perfluoroalkoxy alkane (PFA) capillary (0.50 mm diameter, 1 m length) through a cross mixer under inert atmosphere (Table 2, entries 1–6 & 8–11). From all these experiments, it was observed that the reaction time could surprisingly be decreased to 3.93 s from 5 min in flask (Table 2, entry 3) at a total flow rate of 3 ml/min to attain the identical chemical performance of the desired product **3** in 67% yield and the side products **4** & **5** in 5% & 21%, respectively, which is consistent with the results of the reaction in flask (entry 8, Table 1). Notably, the use of larger diameter PFA capillary (1.0 mm) significantly decreased the yield of product **3** (52%), presumably owing to lowered mixing efficiency[1,4] (Table 1, entry 7). Excellent mixing efficiency throughout the confined reaction space[1] of the microfluidic reactor, which is provided by a high surface-area-to-volume ratio, lowered the synthesis time to several seconds (3.9 s) from several minutes (5 min).

Table 2. Continuous-flow synthesis of *α*-phosphonyloxy ketones from *α*-dicabonyl compounds and trialkyl phosphites in a capillary reactor[a]

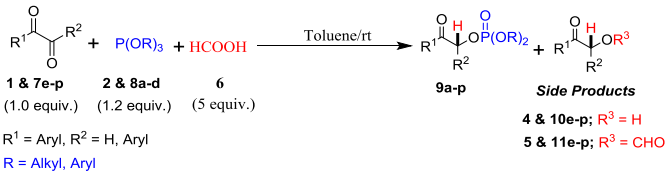


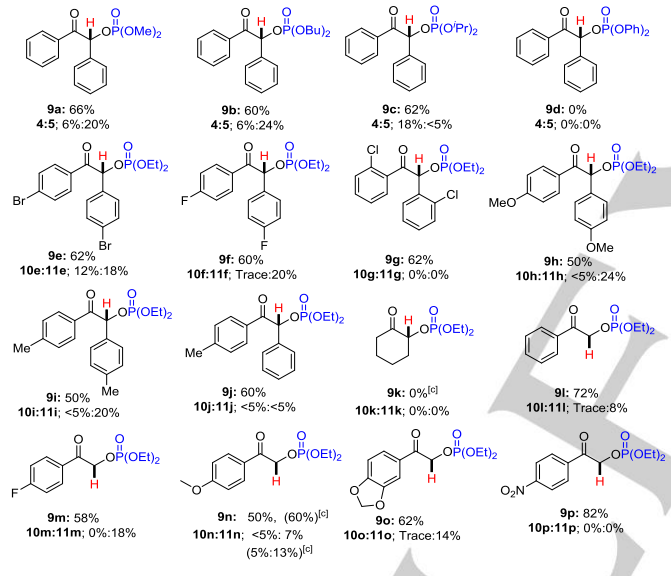
Entry	Solvent (Conc. (M))	Flow rate	Residence time t^R [s]	Yield (%) 3:4:5 (%)[b]
1	Toluene (0.2)	3 ml/min	3.93	30:10:20
2	Toluene (0.1)	3 ml/min	3.93	44:8:18
3	**Toluene (0.067)**	**3 ml/min**	**3.93**	**67:5:21**
5	Toluene (0.067)	1.5 ml/min	7.85	67:5:25
6	Toluene (0.067)	4.5 ml/min	2.62	40:8:14
7[c]	Toluene (0.067)	3 ml/min	15.71	52:7:26
8	DMF (0.067)	3 ml/min	3.93	64:5:19
9	DMSO (0.067)	3 ml/min	3.93	40:10:5
10	DCM (0.067)	3 ml/min	3.93	45:5:15
11	THF (0.067)	3 ml/min	3.93	60:5:15

[a] Reaction conditions: Perfluoroalkoxy alkane (PFA) capillary (0.50 mm diameter, 1 m length) was used with 0.067 M of **1** (1 mmol scale) in solvent (total volume). 1.2 equiv. of **2** with respect to **1**, and 5.0 equiv. of acids were found to be optimal. RT = 23–26 °C. [b] Isolated yields. [c] PFA capillary with 1.0 mm diameter, 1 m length used.

To confirm the synthetic generality of this chemistry, the substrate scope of *α*-phosphonyloxy ketones was examined using a wide range of *α*-dicabonyl compounds and various trialkyl (aryl) phosphites under the optimized flow reaction conditions (Scheme 2). The new synthetic methodology worked very well with various trialkyl phosphites (**8a–c**) except aromatic phosphite (**8d**). The corresponding products of *α*-phosphonyloxy ketones (**9a–c**) were obtained in good yields (60-66%) with low yields (0-24%) of side products in 3.93 s residence time. In the cases where various halogen and alkyl substituted *α*-dicabonyl compounds (**7e–i**) reacted with triethyl phosphite (**2**), the corresponding desired products (**9e–i)** were produced in moderate to good yields (50-62%) with side products in the range of 0–24% yields in 3.93 s of residence time. Additional evaluation of the method was made for regioselective and chemoselective addition of the phosphite. Scheme 2 shows that regioselective addition product (**9j)** was obtained from substrate **7j** in good yield (60%) with no observable reaction from aliphatic diketone (**7k)** either at room temperature or even at 80 °C. The chemoselective addition of triethyl phosphite **2** to various glyoxal derivatives (**7l–p**) was evaluated using DMF solvent with complete solubility of glyoxal derivatives. Phenyl glyoxal (**7l**), halogen (**7m**), and *o*-alkyl substituted phenyl glyoxals (**7n & 7o**)

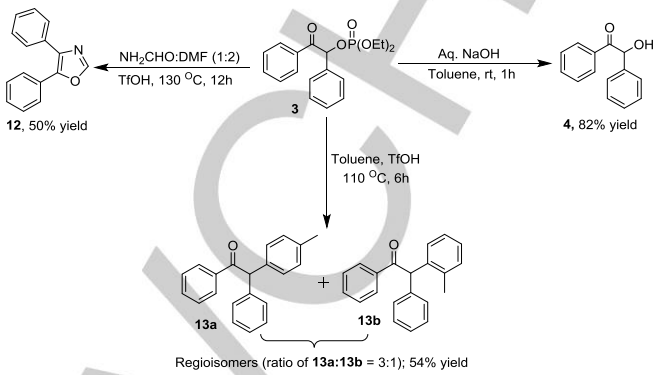
were chemoselectively transformed to their corresponding products (**9l–9o)** in good yields (50-72%). Interestingly, when electron donating substrate (**7n**) was employed at 80 °C under the standard reaction conditions, the yield of the product (**9n**) was improved to 60% from 50% at room temperature with 5% and 13% yields of side products **10n,** & **11n,** respectively, within 3.93 s residence time. Electron-withdrawing group substituted glyoxal **7p** underwent more efficient conversion to the product **9p** in better yield (82%) than the electron donating group substituted *α*-dicabonyl compounds. These results demonstrate that the fast and single-step synthetic chemistry is applicable to diverse *α*-phosphonyloxy ketone analogues, which would be highly useful for manufacturing drug scaffolds[13-15,25-28] in a simple and environmentally benign manner.





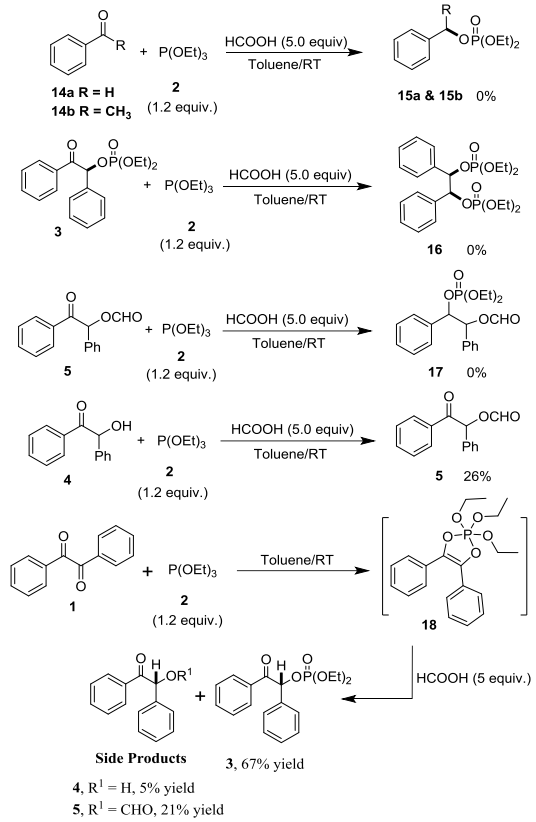
Scheme 2. Continuous-flow synthesis of different α-phosphonyloxy ketones from various α-dicabonyl compounds and trialkyl phosphites in a capillary reactor.[a] [a] Reaction conditions: 0.067 M of **1** (1 mmol scale) in solvent; Perfluoroalkoxy alkane (PFA) capillary (0.50 mm diameter, 1 m length) was used; Flow rate: 3 ml/min; Residence time 3.93 s; RT = 23–26 °C; Isolated yields. [b] DMF was used instead of toluene in the case of substrates **7e, 7g–h & 7l–7p**. [c] Reaction at 80 °C.

Furthermore, the *α*-phosphonyloxy ketone produced can be utilized to form alternative key precursors/scaffolds that are useful for the synthesis of natural products[25,27] and active pharmaceutical ingredients (APIs)[13-15,26,28] (Scheme 3). First, *α*-phosphonyloxy ketone **3** was unmasked in batch to form acyloin *via* deprotection of phosphate moiety (Scheme 3). Benzoin **4** as a precursor of oxaprozine drug was formed in 82% yield under basic condition (aq. NaOH) at room temperature. Secondly, oxazole scaffold **12** with various biological properties was obtained from **3** in 50% yield by batch process with formamide in the presence of triflic acid (TfOH) at 130 °C, as a new synthetic route over a few reports[25-27] (Scheme 3). Thirdly, *α,α'*-diarylated carbonyl compounds (**13a** & **13b**) as key intermediates of drug[28] were also obtained in 54% yields from **3** as regioisomers by treating with triflic acid (TfOH) in the presence of toluene at 110 °C *via* the new synthetic method (Scheme 3).



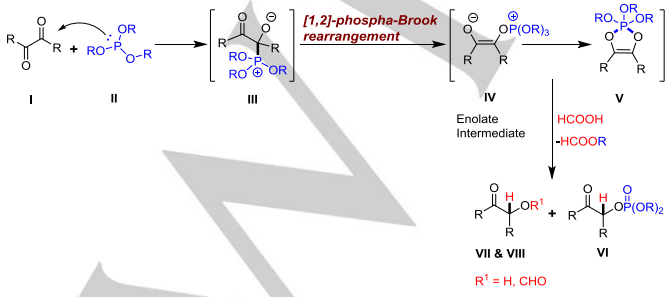
Scheme 3. Applications of α-phosphonyloxy ketone (**3**) to produce alternative drug precursors in batch.[a] [a] Reaction conditions; DMF (Dimethylformamide), TfOH (1.5 equiv.); rt = 23–26 °C; Isolated yields.

Given the successful synthesis of *α*-phosphonyloxy ketones in this methodology, it is very clear that [1,2]-phospha-Brook rearranged products were formed without producing the possible second addition of trialkyl phosphite to both the carbonyl groups present in *α*-dicarbonyl compounds. However, in order to understand the reaction mechanism in detail, a series of control experiments were performed in batch using optimized reaction condition (Scheme 4). Initially, two experiments were carried out in which benzaldehyde **14a** or aceto phenone **14b** were treated to standard condition and the reaction was monitored by TLC. In both reactions, no product was observed even after 12 h. These experiments clearly indicate that the need of aroyl (ArCO) moiety in the carbonyl substrate in promoting analogous [1,2]-phospha-Brook rearrangement to produce the desired C-O-P system. Further, a few experiments were also performed in which the formation of three possible products (**3**-**5**) in this methodology were treated to standard condition in batch. When substrate **3** or **4** was subjected to optimal condition, the corresponding expected products **16** or **17**, respectively were not observed even after 6 h. Further, when benzoin **4** was treated to standard condition, oxy-formylation of benzoin product **5** was obtained in 26% yield after 6 h. Lastly, a typical experiment was performed in which benzil **1** was subjected to triethyl phosphite **2** in toluene at room temperature, stirred about 30 min and the reaction was monitored by ^{1}H NMR spectroscopy. In this case, the formation of a pentavalent phosphorous complex[29] (**18**) with the presence of benzil starting material was observed. However, when this reaction mixture was treated with formic acid **6** (5.0 equiv.) for 5 min, the corresponding products **3**, **4**, & **5** were isolated in 67%, 5%, & 21% yields, respectively, which were found to be almost identical to the batch process. From all these experiments, we conclude that oxy-formylation of benzoin product **5** was derived from benzoin **4** which was produced from complex **18** in the presence of formic acid.



Scheme 4. Control experiments in batch to understand the reaction mechanism

Based on the literature reports[29-31] and control experiments, a plausible mechanism has been proposed as shown in scheme 5. Initially, nucleophilic addition of trialkyl phosphite (**II**) to more reactive carbonyl moiety present in *α*-dicarbonyls (**I**) that generates a zwitterion intermediate (**III**). This intermediate **III** could further undergo rearrangement which is analogous to [1,2]-phospha-Brook rearrangement triggered by aroyl (ArCO) group to produce the an unstable enolate intermediate (**IV**). This unstable intermediate **IV** could further produce intermediate **V** *via* intramolecular attack of oxy anion to phosphonium ion. Then, intermediates **IV** & **V** can produce the *α*-phosponyloxy ketone **VI** product along with expulsion of side products **VII** & **VIII** in the presence of formic acid.



Scheme 5. Plausible reaction mechanism for the synthesis of *α*-phosponyloxy ketone

In summary, we developed a fast-single step approach for the synthesis of *α*-phosphonyloxy ketones as drug scaffolds through a highly reactive species *i.e.,* 1,2-dicarbonyls that combine readily with trialkyl phosphites and formic acids in batch as well as perfluoroalkoxy alkane (PFA) capillary microreactor at room temperature. The use of highly reactive starting reagent led to significantly shorten the synthesis time to minutes in batch, seconds in microreactor, along with inevitable formation of by-products. In particular, this approach was broadly demonstrated for synthesis of various *α*-phosphonyloxy ketone derivatives in moderate to good yields (50-82%) in continuous-flow within 3.93 s residence time in a simple, fast, and environmentally benign manner. Further, the obtained *α*-phosphonyloxy ketone converted to form three alternative key precursors/scaffolds that are useful for the synthesis of natural products and active pharmaceutical ingredients (APIs).

Acknowledgements

We gratefully acknowledge the support from the National Research Foundation (NRF) of Korea grant funded by the Korean government (NRF-2017R1A3B1023598).
Author contributions: B. T., D. K. designed the study and wrote the manuscript. B. T., S. V., and S. Y. performed experiments and analyzed data.

Conflict of interest

The authors declare no conflict of interest.

Keywords: Organophosphates • Flow-chemistry • Fast reaction (3.93 s) • 1,2-phospha-Brook rearrangement • Drug scaffolds

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10.1002/ejoc.201901655

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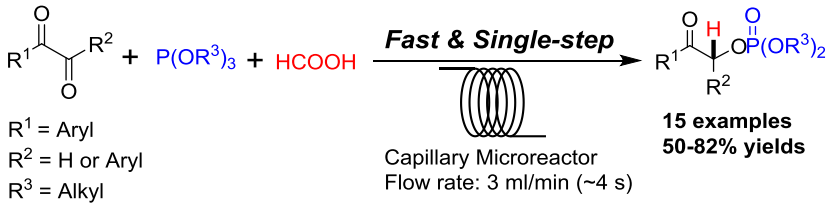

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Fast-Synthesis of α-phosphonyloxy ketones as Drug Scaffolds in a Capillary Microreactor

A room temperature approach for the fast single-step synthesis of α-phosphonyloxy ketone, a drug scaffold, has been developed which involves a highly reactive species *i.e.,* 1,2-dicarbonyls that combine readily with trialkyl phosphites and formic acids in continuous-flow. A wide range of 1,2-dicarbonyl derivatives were smoothly transformed to their corresponding α-phosphonyloxy ketones in moderate to good yields (50-82%) in continuous-flow with the flow rate of 3 ml/min (t^R = ~4 s). Further, the α-phosphonyloxy ketones produced can be utilized to form alternative key precursors/scaffolds of natural products and active pharmaceutical ingredients (APIs).