Budapest University of Technology and Economics
Department of Organic Chemistry and Technology

MICROWAVE-ASSISTED MULTICOMPONENT SYNTHESES OF HETEROCYCLIC PHOSPHONATES

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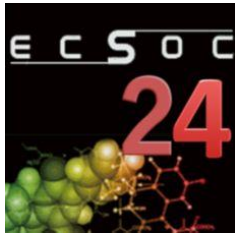
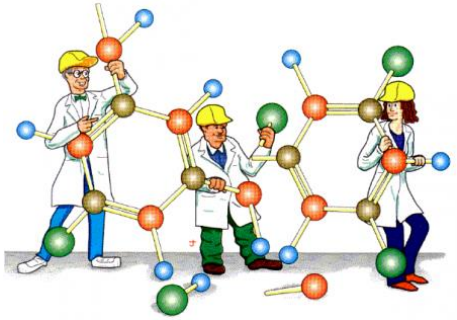
Bettina Rávai, Kármen Emőke Szabó and Franc Perdih



24th International Electronic Conference on Synthetic Organic Chemistry
15 November - 15 December 2020

Importance of phosphorus compounds

organic chemistry



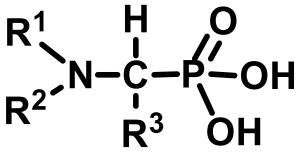
inorganic chemistry

medicinal chemistry

agriculture

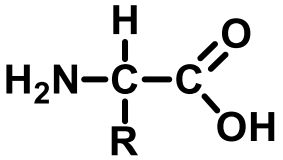
plastic industry

α-Aminophosphonates



α-aminophosphonic acids

structural analogy



α-amino acids

antibiotics
Phos. Heterocycles I. **2009**, *20*, 31.

antitumour agents
Curr. Med. Chem. Anticancer Agents **2001**, *1*, 301.

antiviral species
J. Antimicrob. Chemother. **1999**, *43*, 211.

anti-metabolites
Biochemistry, **2002**, *41*, 12320.

Biological activity

antihypertensives
Tetrahedron **1999**, *55*, 12237.

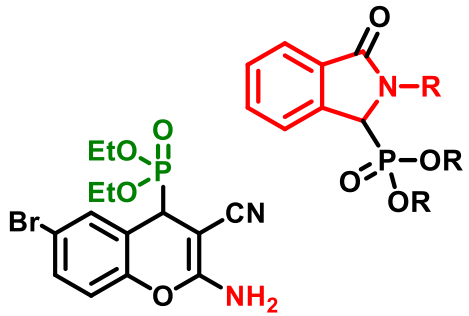
inhibitors of GABA-receptors
J. Med. Chem. **1994**, *37*, 158.

enzyme inhibitors
J. Med. Chem. **1989**, *32*, 1652.

pesticides, herbicides
J. Med. Chem. **1987**, *30*, 1603.

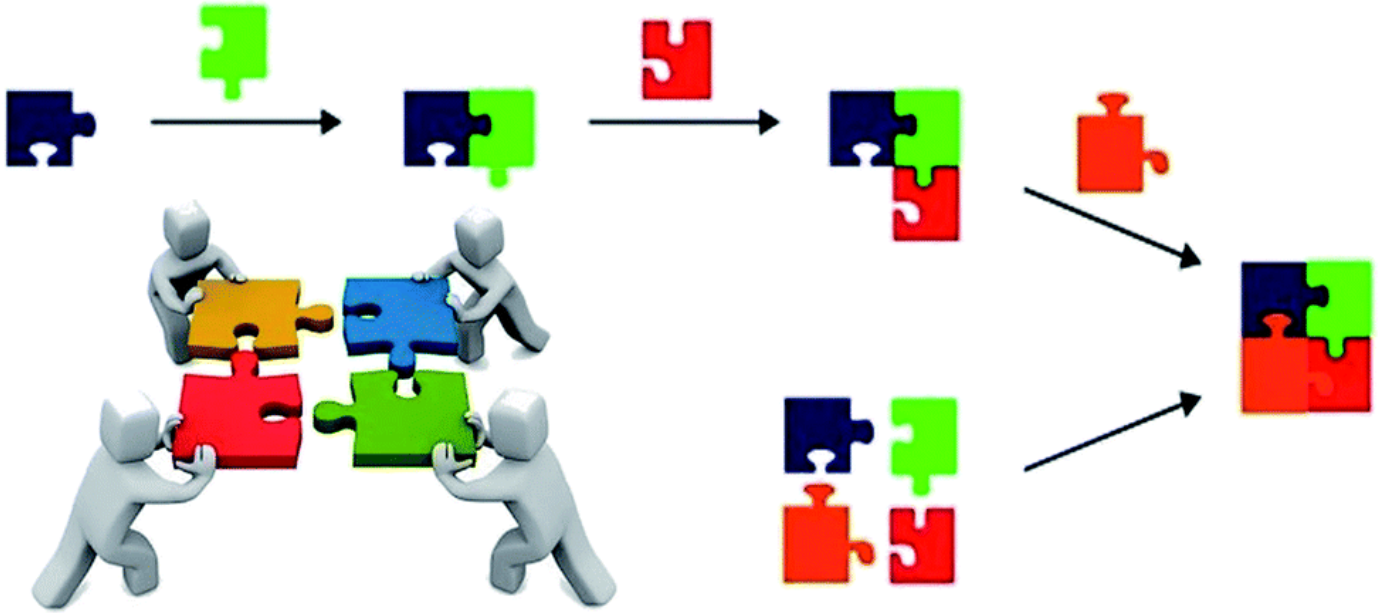
Heterocyclic compounds

- Antihypertensives
- Inflammatories
- Antitumour agents
- Anti-malarial agents
- Antibacterial agents
- Anti-HIV drugs



Kappe, C. O.; Stadler, A. The Biginelli dihydropyrimidine synthesis in Overman L. E. (ed.) *Organic Reactions*, Wiley, **2004**
Sandhu, S.; Sandhu, J. S.. *Arkivoc* **2012**, 66.

Multicomponent reactions



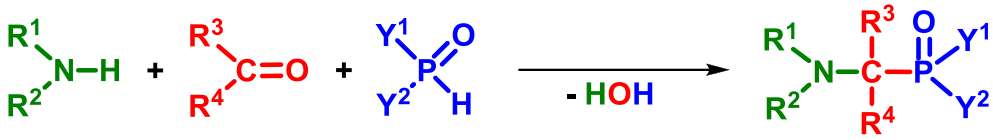
Advantages:

- Easily accessible, inexpensive starting materials
- Fast and simple accomplishment
- Generally high atomic efficiency
- Ability to save time and energy
- Formation of Molecular Libraries

Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.*, **2012**, *112*, 3083.
Müller, T. J. J. (Ed.), Multicomponent Reactions 1. In Science of Synthesis, Thieme, Stuttgart, 2014.

Kabachnik-Fields (phospha-Mannich) reaction

M. I. Kabachnik



Kabachnik, M. I.; Medved, T. Y. *Dok. Akad. Nauk. SSSR* **1952**, *83*, 689.

Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528.

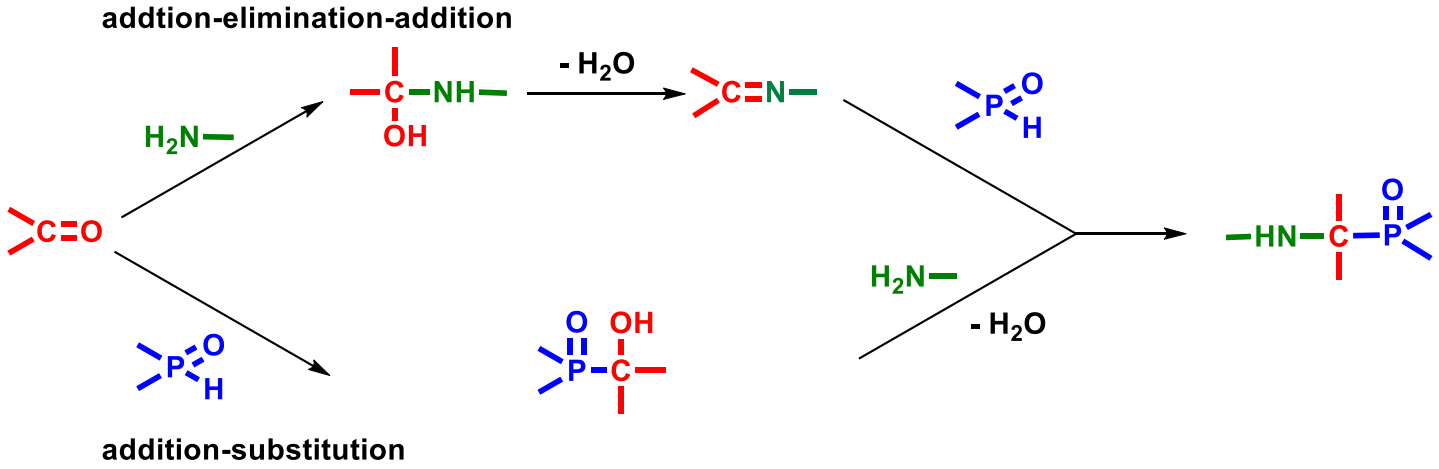
E. K. Fields

Catalyst: $SnCl_4$, $ZnCl_2$, $InCl_3$, $TaCl_5$-SiO_2, $Mg(ClO_4)_2$, GaI_3, $Bi(NO_3)_3$, $BiCl_3$, SmI_3, $Yb(OTf)_3$, $La(OTf)_3$, $Sm(OTf)_3$, $In(OTf)_3$

Solvents: dichloromethane, tetrahydrofuran, ethanol, acetonitrile, etc.

Keglevich, G.; Bálint, E. *Molecules* **2012**, *17*, 12821.

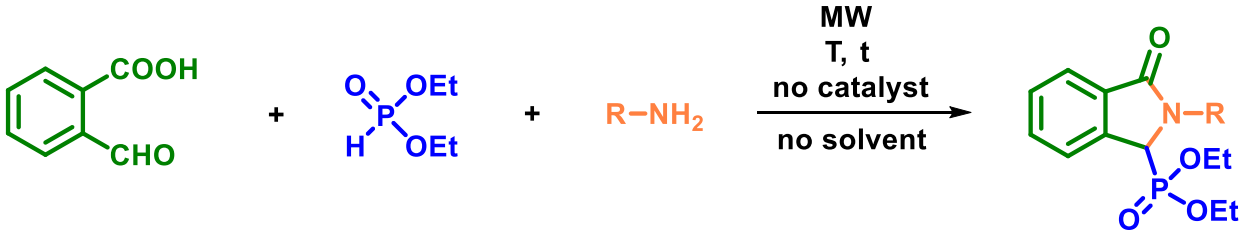
Reaction mechanism



Cherkasov, R. A.; Galkin, V. I. *Russ. Chem. Rev.*, **1998**, *67*, 857.

Synthesis of isoindolin-1-one-3-phosphonates by Kabachnik-Fields reaction followed by cyclization

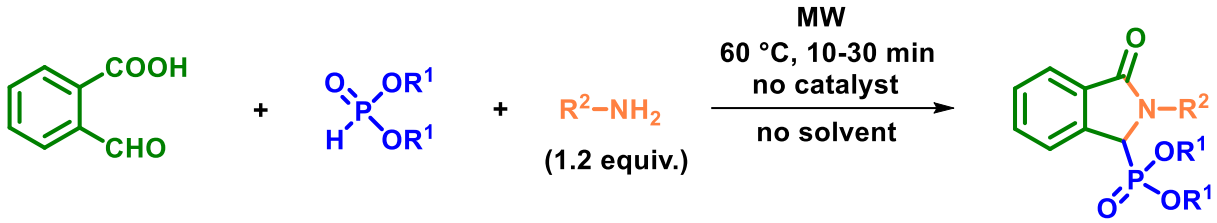
Study of the reaction of 2-formylbenzoic acid, diethyl phosphite and primary amines

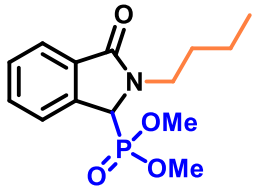


Entry	R	Amine [equiv.]	T [°C]	t [min]	Conversion[a] [%]	Yield[b] [%]
1	Bu	1	rt	180[c]	77	–
2	Bu	1	40	10	61	–
3	Bu	1	60	10	85	–
4	Bu	1	60	20	90	–
5	Bu	1	60	30	93	–
6	Bu	1.2	60	10	100	94
7	[c]Hex	1.2	60	10	84	–
8	[c]Hex	1.2	60	20	93	–
9	[c]Hex	1.2	60	30	100	84
10	Bn	1.2	60	10	90	–
11	Bn	1.2	60	20	100	90

[a]On the basis of GC. [b]After column chromatography. [c]No change after longer reaction time.

Extension of the reaction





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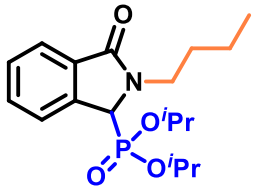

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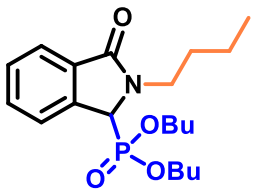

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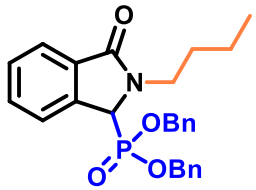

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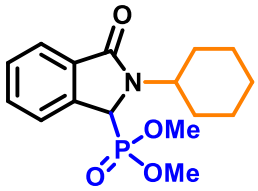

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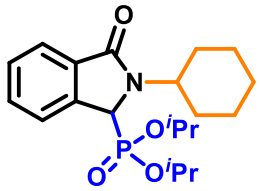

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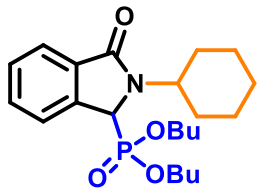

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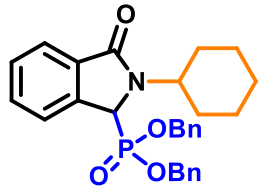

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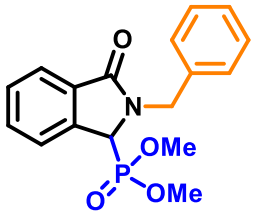

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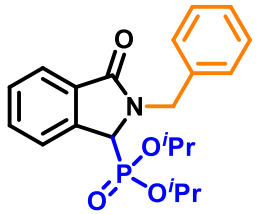

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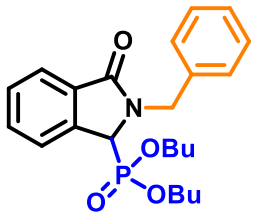

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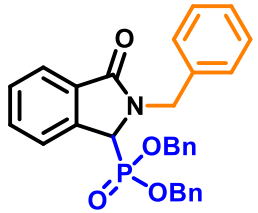
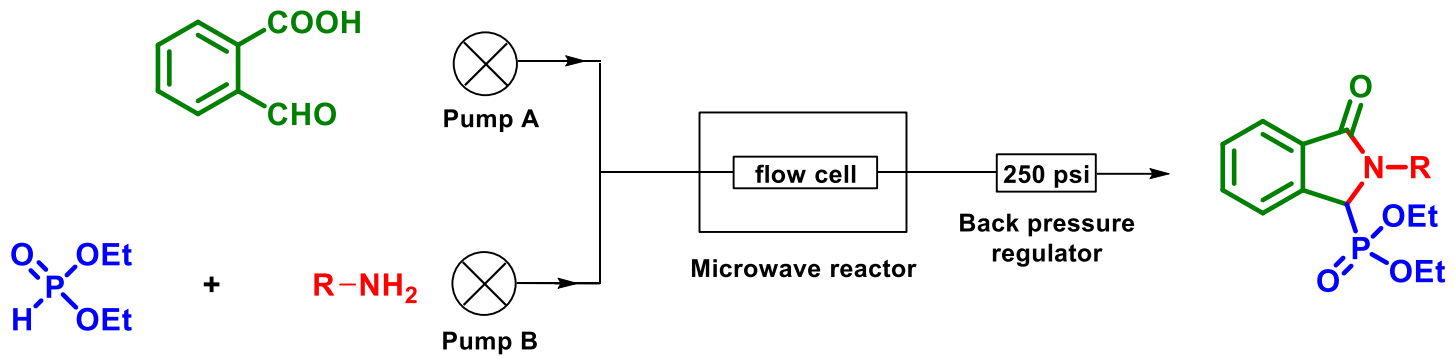


84%

13 new derivatives

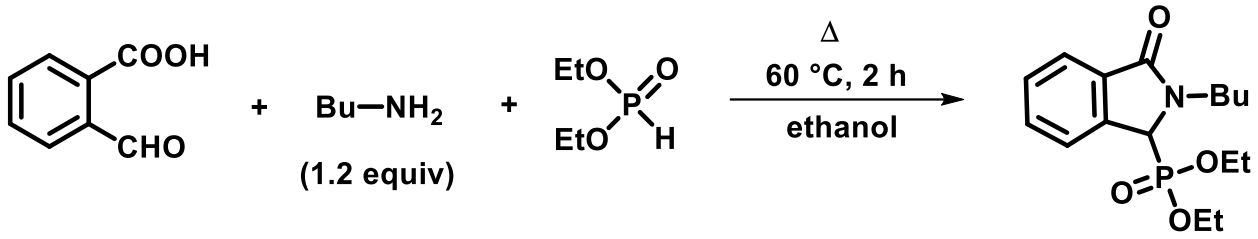
Continuous flow reaction of 2-formylbenzoic acid, diethyl phosphite and primary amines



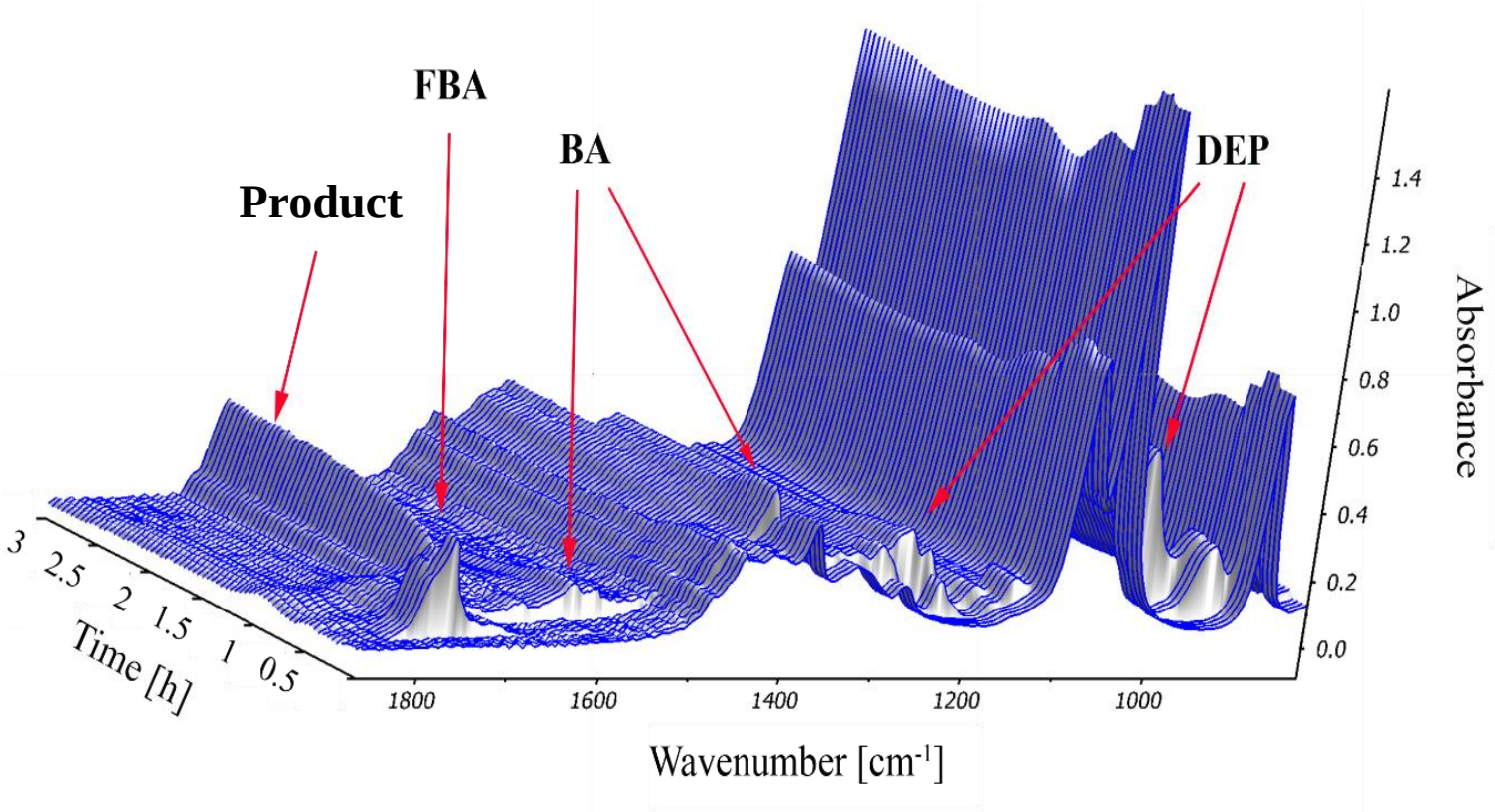
Entry	R	Amine [equiv.]	DEP [equiv.]	Flow rate [mL/min]	τ [min]	Conversion[a] [%]	Yield[b] [%]
1	Bu	1.2	1	0.70	10	43	–
2	Bu	1.2	1	0.35	20	52	–
3	Bu	1.2	1	0.25	30	56	–
4	Bu	1.5	1	0.35	20	70	–
5	Bu	2.0	1	0.35	20	73	–
6	Bu	1.5	1.2	0.35	20	81	–
7	Bu	1.5	1.5	0.35	20	95	–
8	Bu	1.5	1.5	0.25	30	100	95
9	[c]Hex	1.5	1.5	0.15	45	100	84
10	Bn	1.5	1.5	0.18	40	100	91

[a]On the basis of GC. [b]Isolated yield.

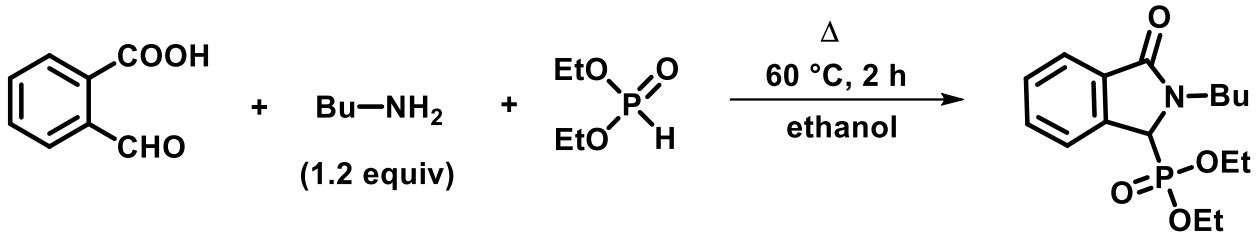
Study on the condensation of 2-formylbenzoic acid, butylamine and diethyl phosphite by in situ FT IR spectroscopy



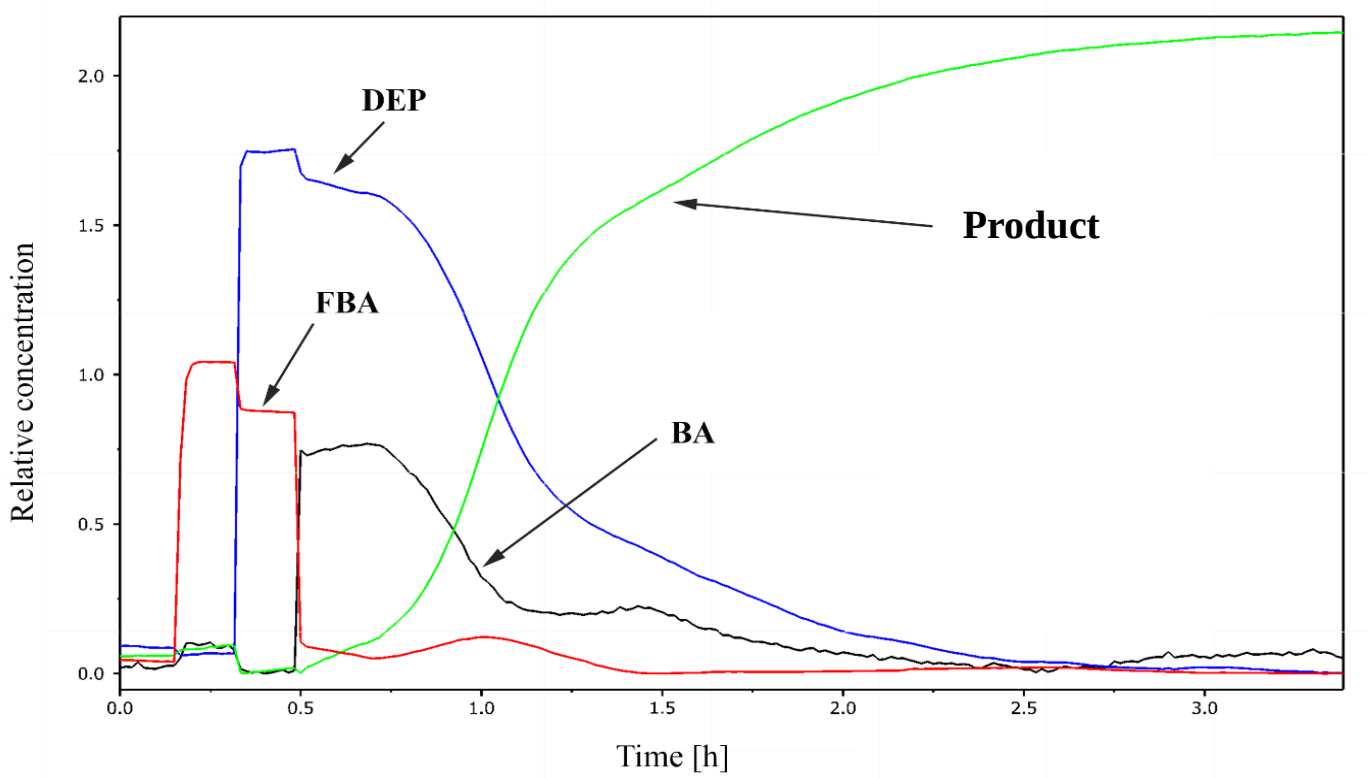
A segment of the time-dependent IR spectrum of the condensation



Study on the condensation of 2-formylbenzoic acid, butylamine and diethyl phosphite by in situ FT IR spectroscopy

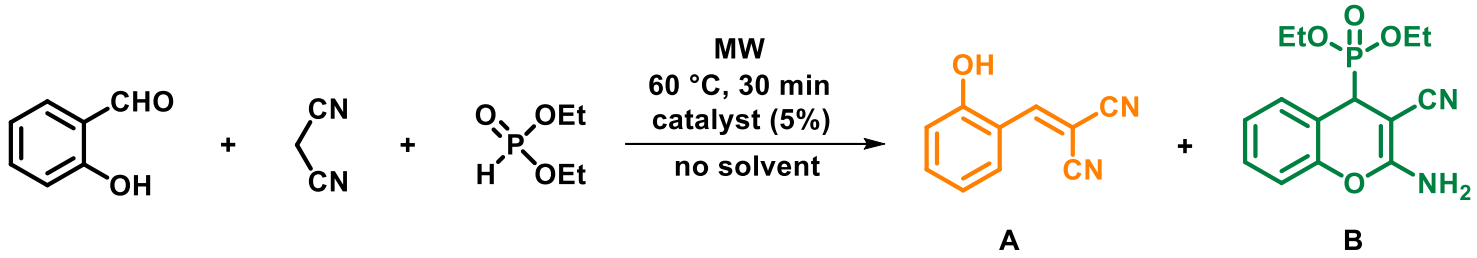


Concentration profiles of the reaction components in the condensation

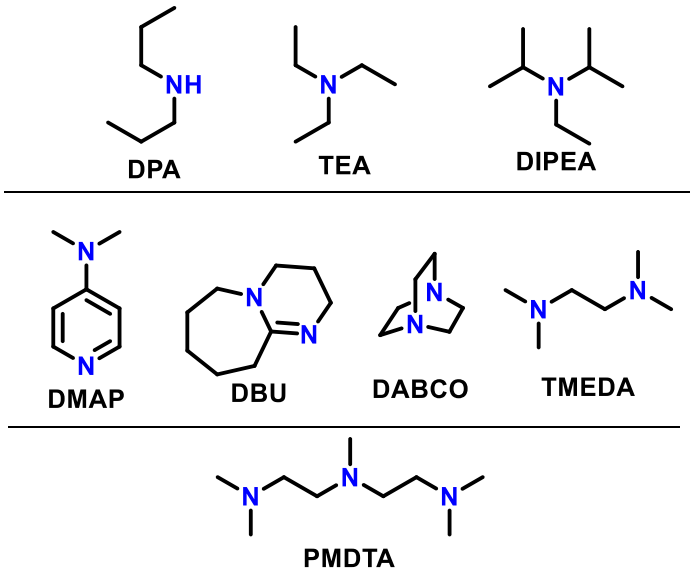


Synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonate derivatives

Study of the reaction of salicylaldehyde, malononitrile and diethyl phosphite using basic catalysts

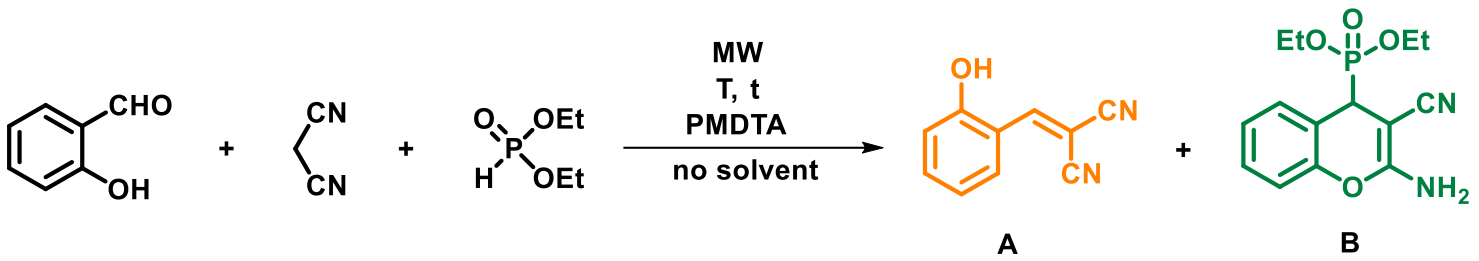


Entry	Catalyst (5 mol%)	Composition [%][a] A	B
1	DPA	65	35
2	TEA	62	38
3	DIPEA	58	42
4	DMAP	73	27
5	DBU	59	41
6	DABCO	47	53
7	TMEDA	42	58
8	PMDTA	14	86
9[b]	PMDTA	65	35
10[c]	PMDTA	70	30



[a]Based on HPLC (254 nm).
[b]The reaction was performed in EtOH.
[c]The reaction was performed in acetonitrile.

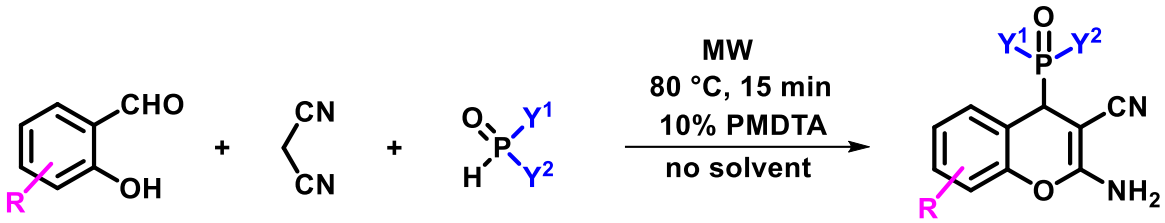
Optimization of the reaction conditions

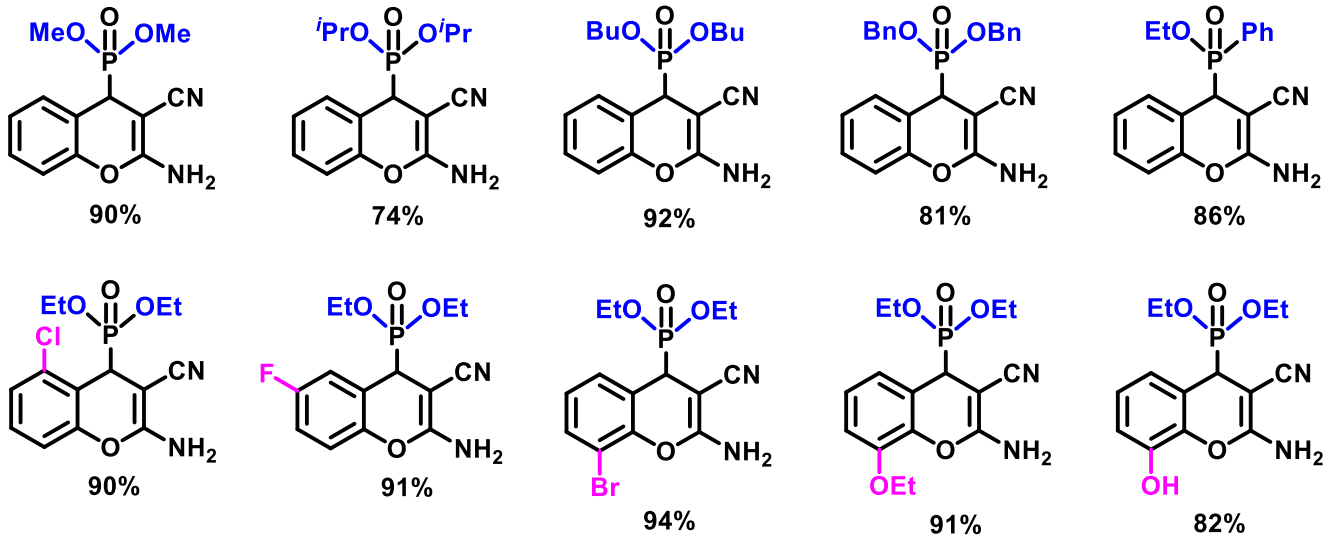


Entry	PMDTA [%]	T [°C]	t [min]	Composition [%][a] A	Composition [%][a] B	Yield [%][b]
1	5	60	30	14	86	–
2	5	60	45	11	89	–
3	10	60	5	18	82	–
4	10	60	10	11	89	–
5	10	60	15	0	100	92
6	5	80	5	21	79	–
7	5	80	10	15	85	–
8	5	80	15	0	100	93

[a]Based on HPLC (254 nm).
[b]After column chromatography.

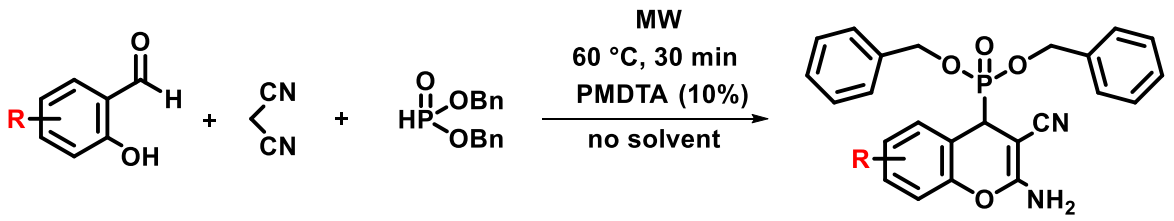
Extension of the reaction





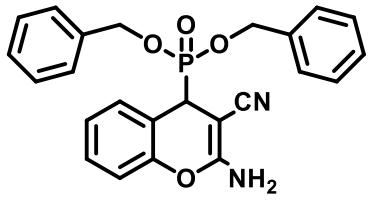
12 derivatives => 9 new

Reaction of dibenzyl phosphite with malonitrile and substituted salicyladehyde



R = H, 5-F, 2-Cl, 3-Br, 3-OEt

R = H, 6-F, 5-Cl, 8-Br, 8-OEt



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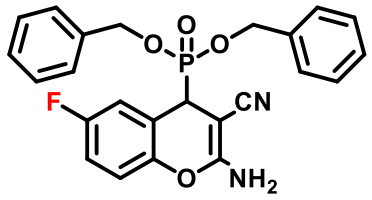

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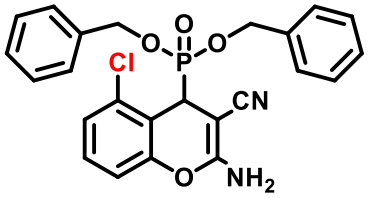

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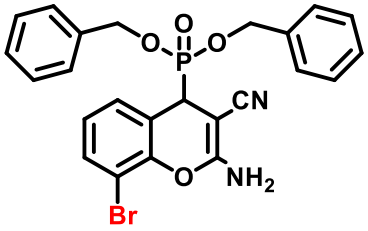

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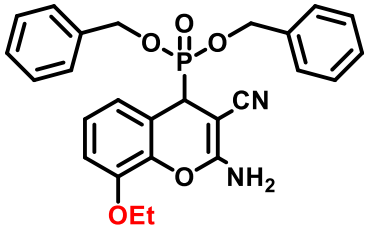
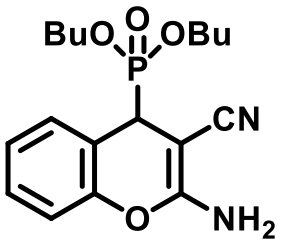
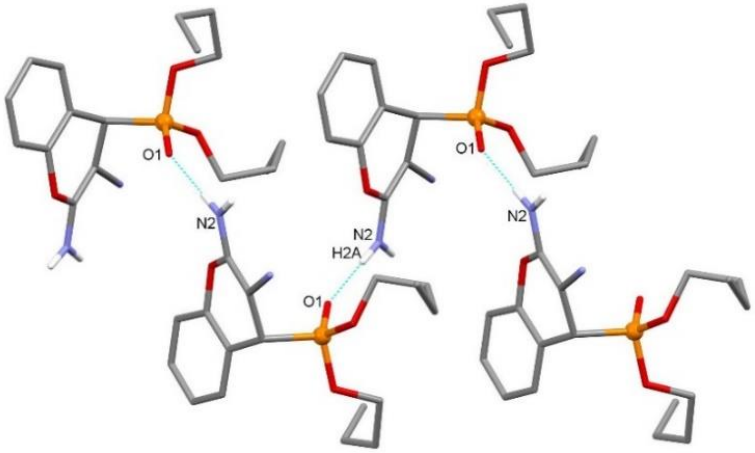


85%

5 new derivatives

- **X-Ray structures of (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates**

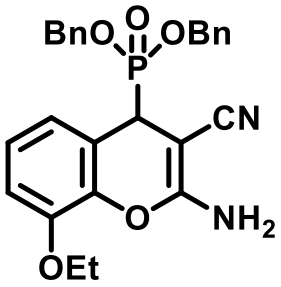


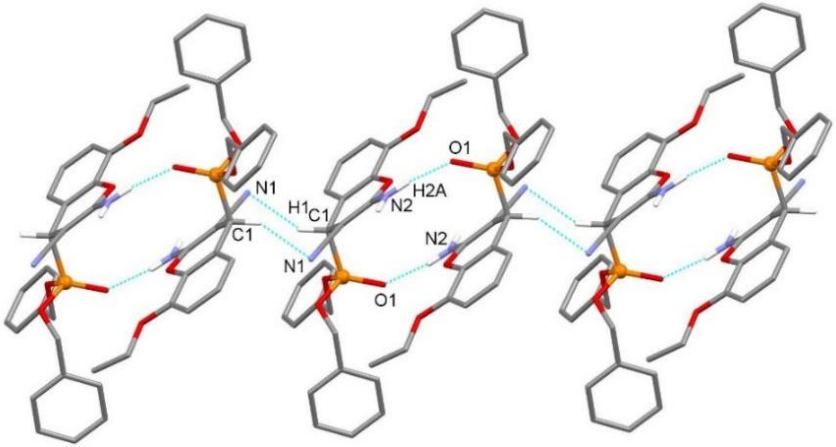


N – H ··· O = P and N – H ··· NC hydrogen bond

+

C – H ··· NC interaction

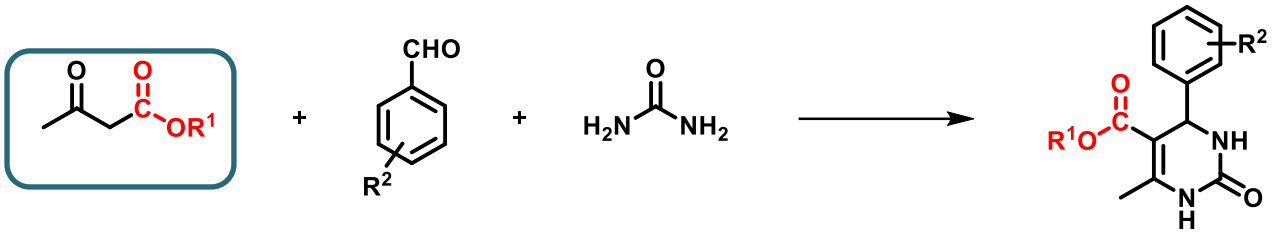




chaines and layers formation

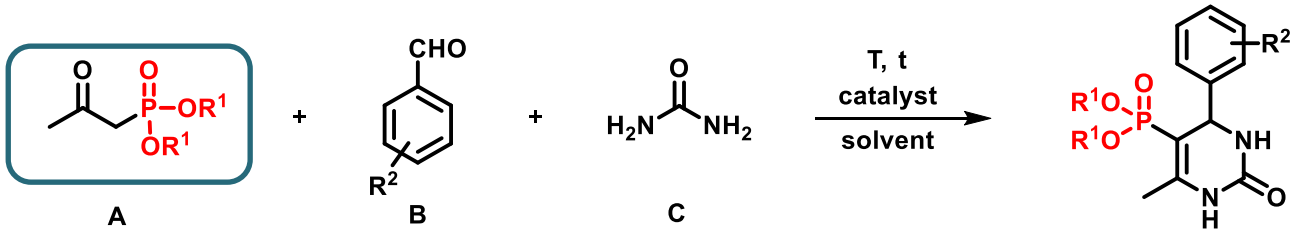
Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one phosphonates by Biginelli reaction

I. Traditional Biginelli reaction



Biginelli, P. *Chem. Ber*. **1891**, *24*, 1317.

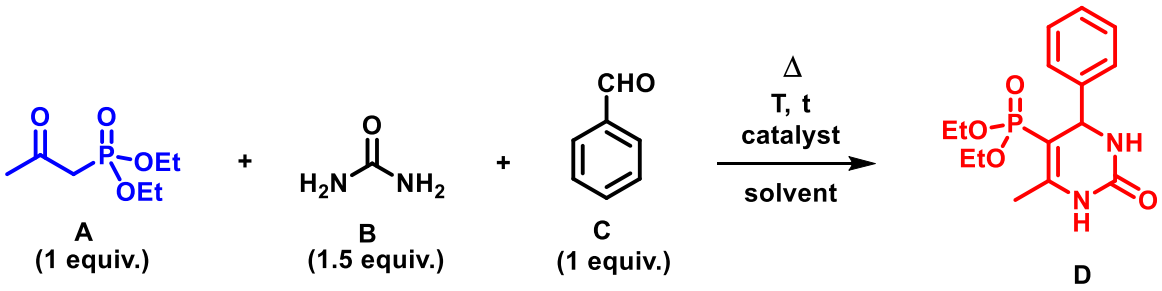
II. Biginelli reaction of β-ketophosphonates



R^1	R^2	A:B:C [equiv]	Catalyst	Solvent	T, t	Yield [%]	Ref.
Me, Et	H, 4-NO_2, 4-Cl, 4-OMe	1:1:1.5	50% PTSA	MeCN	82 °C, 24 h	72-96	[1]
Me, Et	H, 4-NO_2, 4-Cl, 4-Me	1:1:1.5	15% $Zn(OTf)_2$	PhMe	110 °C, 3 h	72-86	[2]
Me, Et	H, 4-F, 4-Cl, 2,4-diCl, 3-Cl, 2-Br, 4-Br, 4-NO_2	1:1:2	5% $Yb(OTf)_3$	PhMe	110 °C, 12 h	23-58	[3]

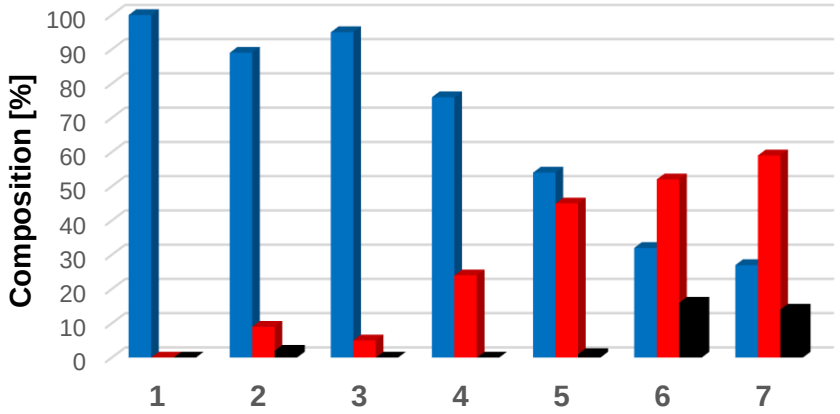
[1] Essid, I.; Touil, S. *Arkivoc* **2013**, 98.; [2] Essid, I.;Lahbib, K.; Kaminsky, W.; Nasr, C. B.; Touil, S. *J. Mol. Struct.* **2017**, *1142*, 130.; [3] Gong, D.; Zhang, L.; Yuan, C. *Heteroatom Chem.* **2003**, *14*, 13.

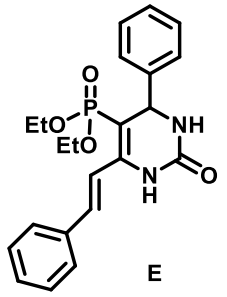
Biginelli reaction of diethyl (2-oxopropyl)phosphonate under thermal heating



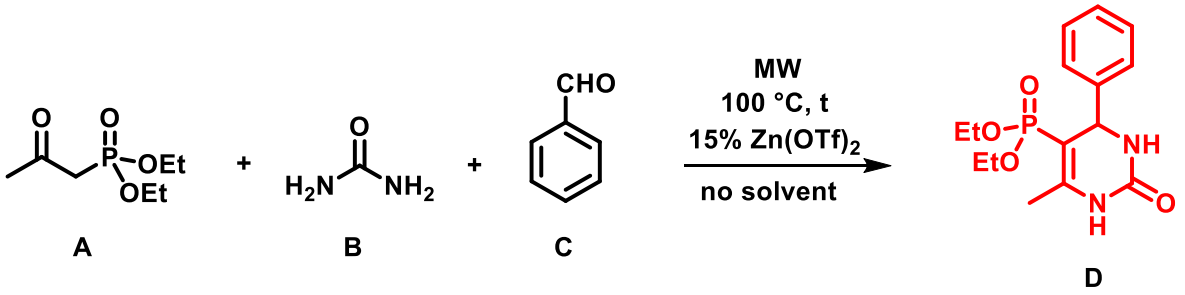
Entry	Catalyst	Solvent	T [°C]	t [h]	Composition [%][a]		
					A	D	E
1	–	MeCN	82	4	100	0	0
2	50% PTSA	MeCN	82	4	89	9	2
3	15% $Sc(OTf)_3$	MeCN	82	4	95	5	0
4	15% $Yb(OTf)_3$	MeCN	82	4	76	24	0
5	15% $Zn(OTf)_2$	MeCN	82	4	54	45	1[b]
6	15% $Zn(OTf)_2$	PhMe	100[c]	2	32	52	16
7	15% $Zn(OTf)_2$	–	100	2	27	59	14

[a]Based on ^{31}P NMR; [b]Composition was not changed at longer reaction time; [c]Decomposition at higher temperature.



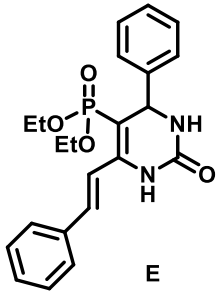


Optimization of the MW-assisted Biginelli-reaction of diethyl (2-oxopropyl)phosphonate

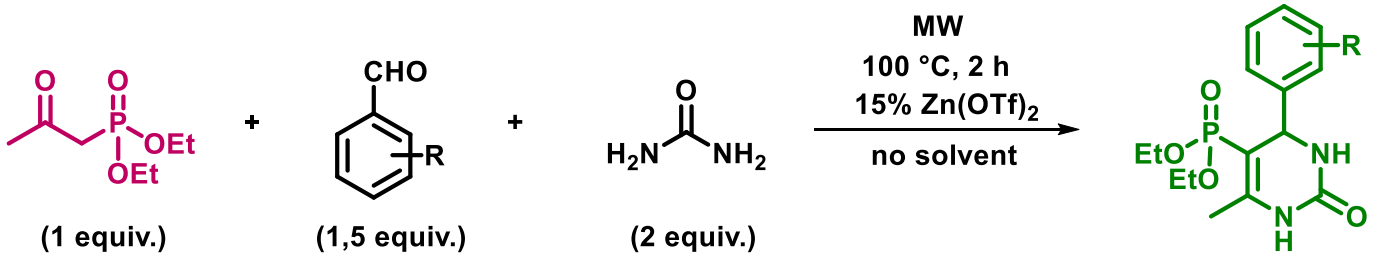


Entry	4a:5a:6a [equiv.]	t [h]	Composition [%][a]			Yield [%][b]
			A	D	E	
1	1:1.5:1	2	28	66	6	–
2	1:1.5:1	4	24	71	5	–
3	1:2:1	2	23	73	4	–
4	1:2:1.2	2	7	84	9	–
5	1:2:1.5	2	0	89	11	75
6	1:2:2	2	0	86	14	–

[a]Based on ^{31}P NMR; [b]After column cromatography.

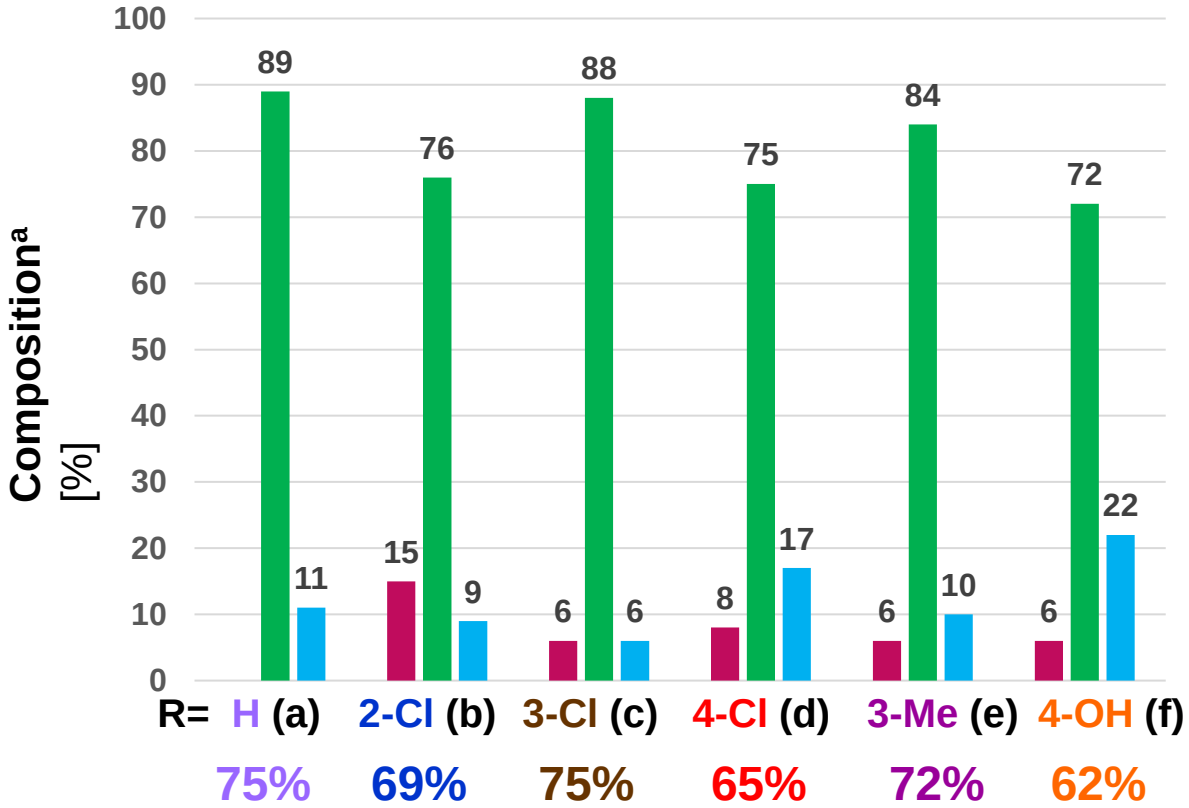


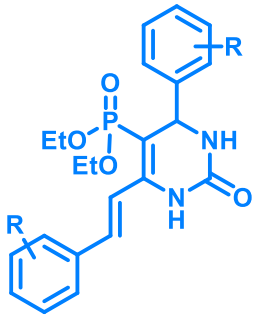
Extension of the MW-assisted Biginelli reaction of diethyl (2-oxopropyl)phosphonate



(1 equiv.) (1,5 equiv.) (2 equiv.)

R= H (a), 2-Cl (b), 3-Cl (c), 4-Cl (d), 3-Me (e), 4-OH (f)



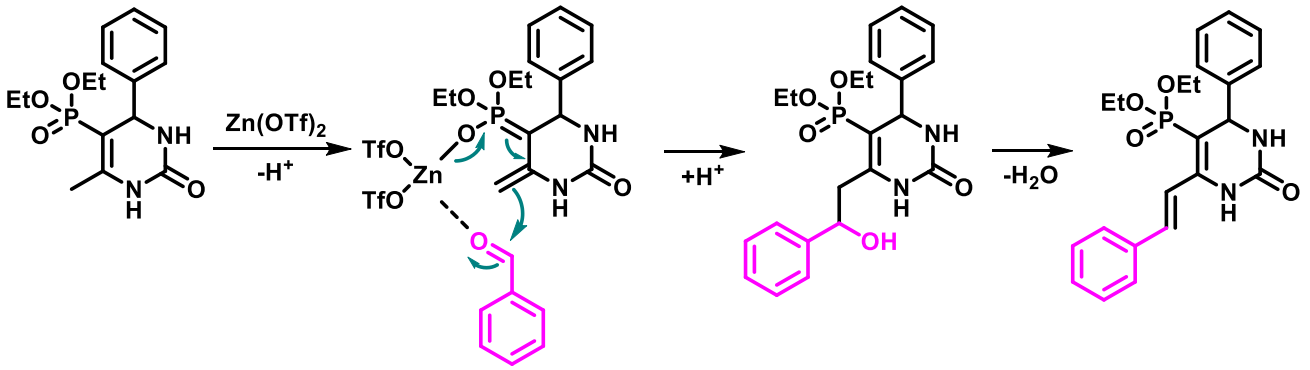


R= H, 2-Cl, 3-Cl, 4-Cl, 3-Me, 4-OH

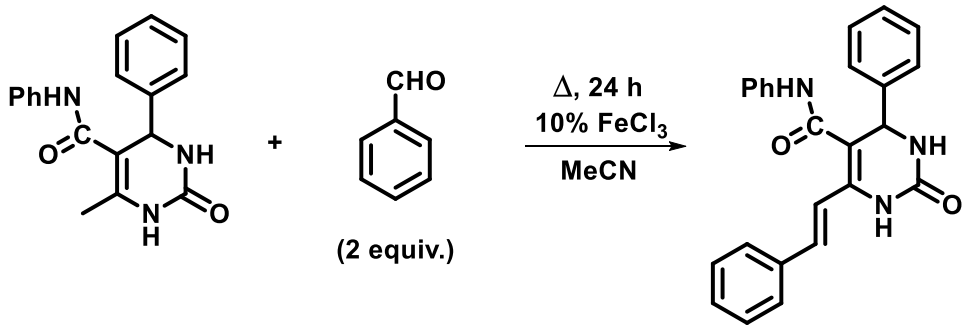
[a]Based on ^{31}P NMR. [b]After column chromatography.

6 derivatives => 3 new

Possible formation of the by-product

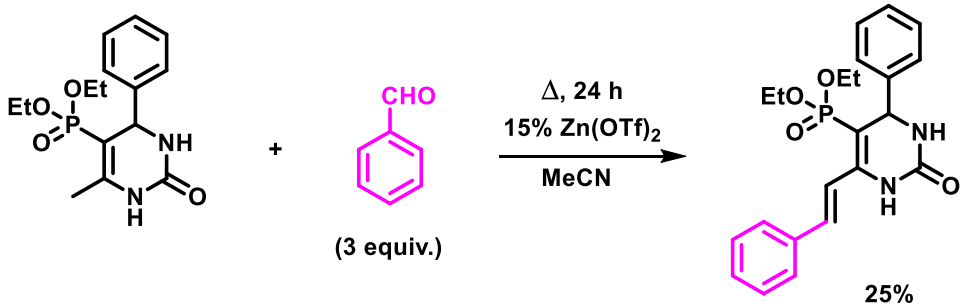


Based on literature references

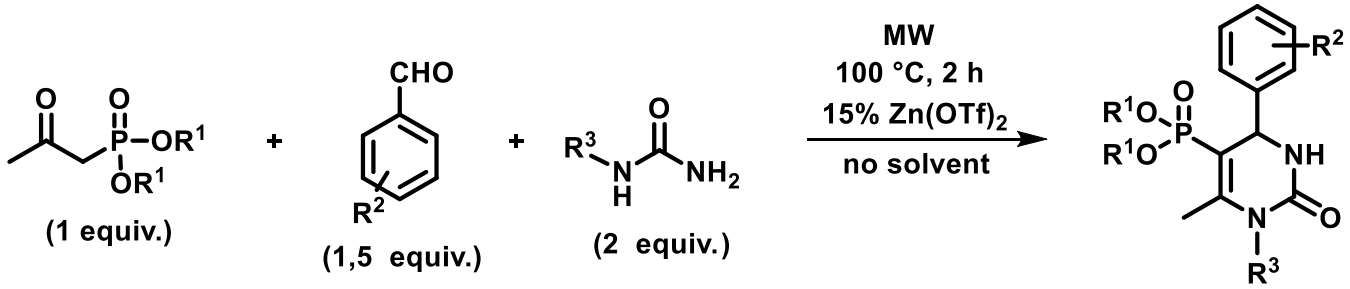


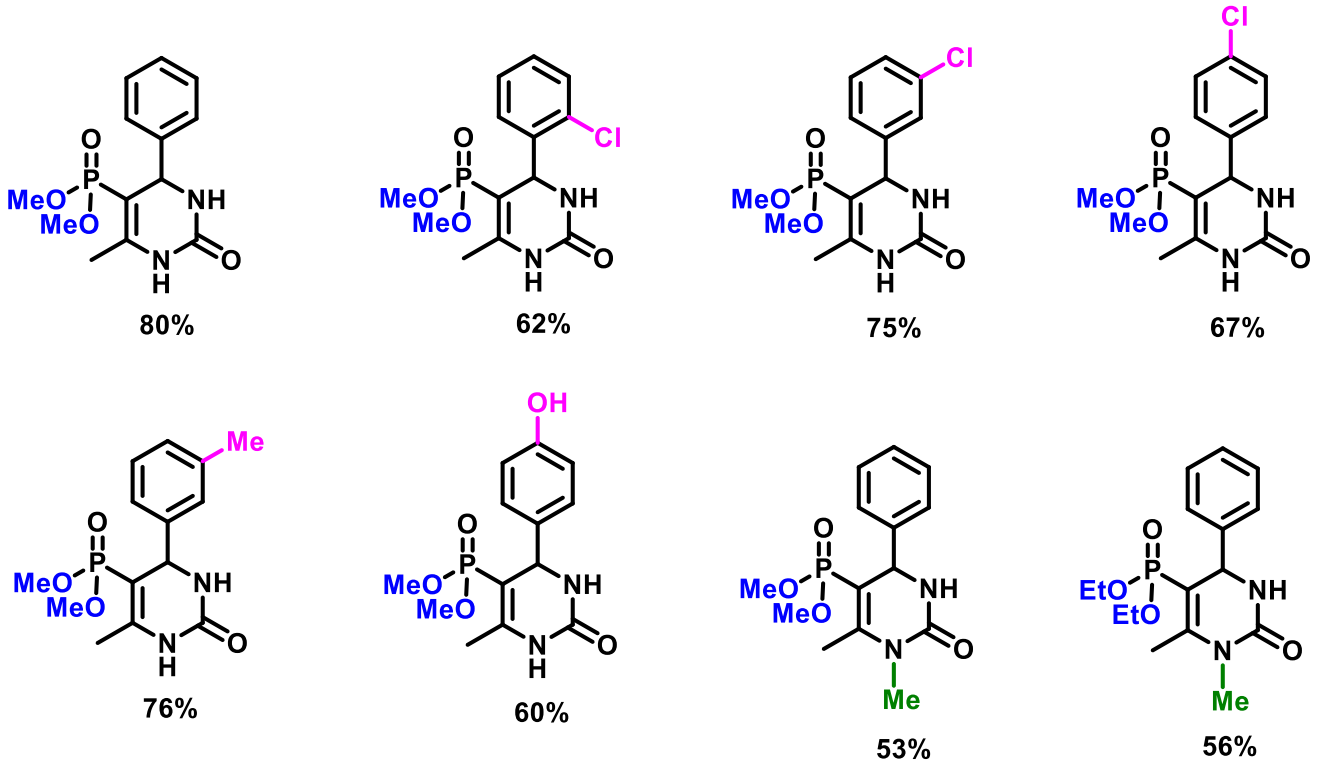
Zhang, L.; Zhang, Z.; Liu, Q.; Liu, T.; Zhang, G. *J. Org. Chem.* **2014**, *79*, 2281.
Zhang, Z.; Zhang, L.; Duan, X.; Yan, X.; Yan, Y.; Liu, Q.; Liu, T.; Zhang, G. *Tetrahedron* **2015**, *71*, 7745.

Pre-experiment for the synthesis of the by-product



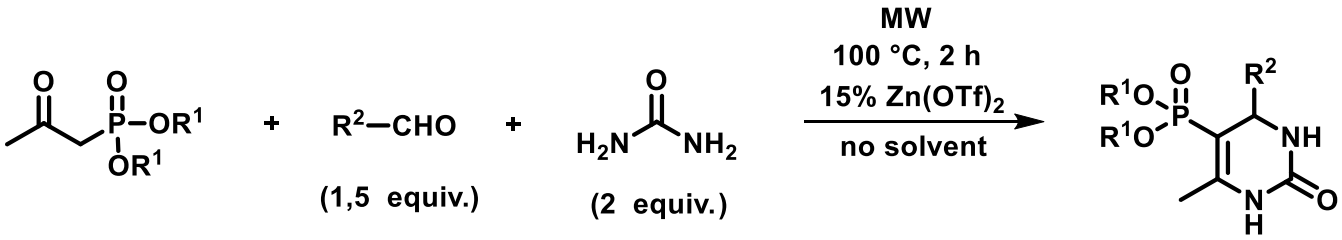
Further extension of the Biginelli reaction

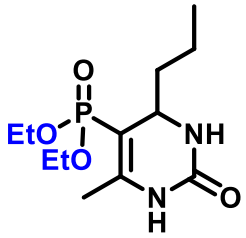


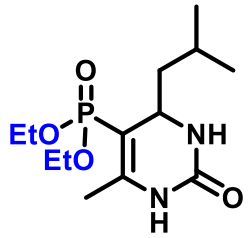


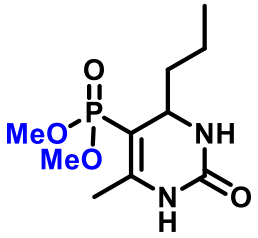
8 derivatives => 6 new

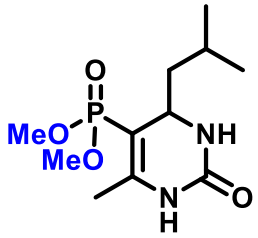
Biginelli reaction with aliphatic aldehydes




41%


43%


43%


42%

4 new derivatives

Bioactivity studies

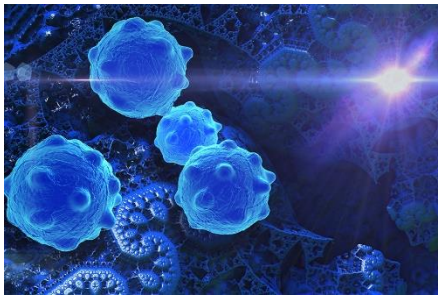
Toxicity study

Non-toxic compounds

Antimicrobial effect

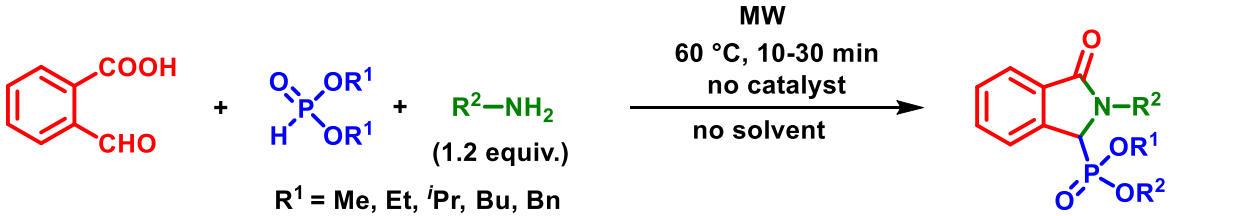
Anti-inflammatory effect

Citotoxicity



Summary

1.) Synthesis of 3-oxoisoindolinylphosphonate derivatives



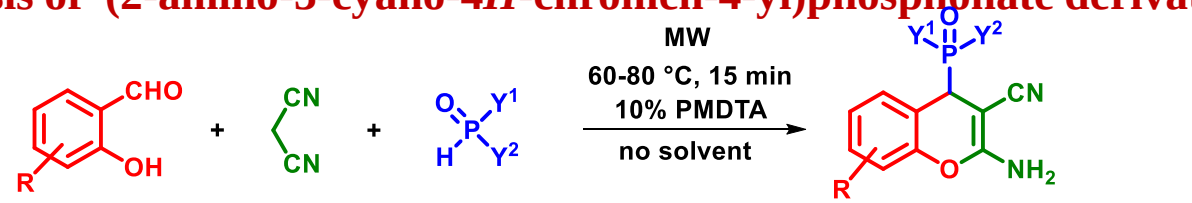
R^1 = Me, Et, ^{i}Pr, Bu, Bn

R^2 = Bu, ^{c}Hex, Bn

80-97%

15 derivatives => 13 new

2.) Synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonate derivatives



R = H, 5-F, 2-Cl, 3-Br, 3-OEt, 3-OH

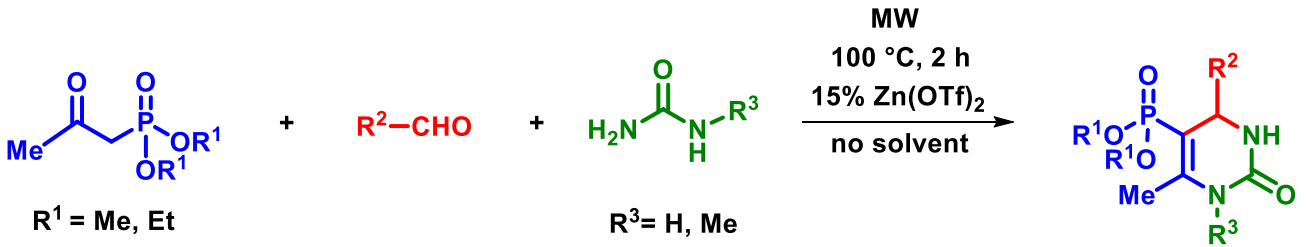
Y^1	OMe	OEt	O^{i}Pr	OBu	OBn	OEt
Y^2	OMe	OEt	O^{i}Pr	OBu	OBn	Ph

R = H, 6-F, 5-Cl, 8-Br, 8-OEt, 8-OH

70-96%

15 derivatives => 11 new

3.) Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one phosphonates



R^1 = Me, Et

R^3= H, Me

R^2 = C_6H_5, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4,3-MeC_6H_4, 4-OHC_6H_4, Pr, ^{i}Bu

41-80%

18 derivatives => 13 new

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