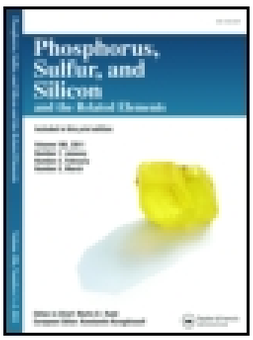


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

One-pot cascade ring enlargement of isatin-3-oximes to 2,4-dichloroquinazolines mediated by bis(trichloromethyl)carbonate and triarylphosphine oxide

Jinjing Qin, Zhenhua Li, Shengzhe Ma, Lixian Ye, Guoqiang Jin & Weike Su

To cite this article: Jinjing Qin, Zhenhua Li, Shengzhe Ma, Lixian Ye, Guoqiang Jin & Weike Su (2020): One-pot cascade ring enlargement of isatin-3-oximes to 2,4-dichloroquinazolines mediated by bis(trichloromethyl)carbonate and triarylphosphine oxide, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2020.1782910

To link to this article: https://doi.org/10.1080/10426507.2020.1782910

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2020.1782910

One-pot cascade ring enlargement of isatin-3-oximes to 2,4-dichloroquinazolines mediated by bis(trichloromethyl)carbonate and triarylphosphine oxide

Jinjing Qin, Zhenhua Li, Shengzhe Ma, Lixian Ye, Guoqiang Jin, and Weike Su

College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P.R. China

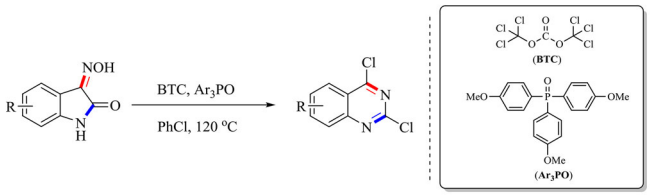
ABSTRACT

An efficient and convenient one-pot cascade synthesis of 2,4-dichloroquinazolines directly from isatin-3-oximes with the addition of bis(trichloromethyl)carbonate and triarylphosphine oxide was developed, leading to substituted quinazolines in moderate to excellent yields. The efficiency of this transformation was demonstrated by compatibility with a range of functional groups. Thus, the method represents a convenient and practical strategy for the synthesis of substituted 2,4-dichloroquinazolines.

ARTICLE HISTORY
Received 20 April 2020
Accepted 11 June 2020

KEYWORDS
2,4-Dichloroquinazoline; isatin-3-oxime; one-pot; ring enlargement; bis(trichloromethyl)carbonate; triarylphosphine oxide

GRAPHICAL ABSTRACT



Introduction

Quinazolines are a privileged class of nitrogen heterocyclic scaffolds, which are present in a wide variety of pharmaceutical products and biological molecules that might be clinical drug candidates.[1,2] Quinazoline derivatives have shown diverse biological activities such as anti-cancer,[3–5] anti-inflammatory[6,7] and antihypertensive activities.[7,8] The huge sales of commercial drugs (e.g., Gefitinib,[9] Erlotinib,[10] Prazosin,[11] Doxazosin[12]) highlight the importance of the quinazoline pharmacophore (Figure 1).

Generally, biological quinazoline derivatives have been synthesized from 2,4-dichloroquinazolines via nucleophilic substitution,[13–15] metal-catalysed coupling[16,17] and/or hydrogenolysis reactions.[18–20] Although novel synthetic strategies for quinazoline derivatives have been proposed and attempted in recent years,[21] 2,4-dichloroquinazolines still play an important role as key intermediates for the synthesis of 2,4-substituted quinazolines. The classical synthetic approach to 2,4-dichloroquinazolines started from the corresponding quinazolinedones or 2,4-dihydroxyquinazolines generated by *o*-aminobenzoic acid derivatives and ureas, chlorinated by phosphoryl chloride ($POCl_3$).[22–26] This chlorination suffers from a long reaction time caused by the poor solubility of the substrates and economic and environmental problems caused by the use of $POCl_3$. 2,4-Dichloroquinazolines can also be prepared in one step from *o*-aminobenzonitrile with diphosgene.[27] However, this method involves toxic diphosgene, harsh reaction conditions and relatively low yields. Coincidentally, we previously reported a method targeting 2,4-dichloroquinazoline from *o*-aminobenzonitrile and triphosgene (Figure 2).[28] On this basis, the development of convenient synthetic methods under eco-friendly reaction conditions for the rapid and straightforward assembly of 2,4-dichloroquinazolines is still highly desirable.

Organophosphorus compounds have been widely employed in organic transformations such as Wittig,[29–31] Mitsunobu,[32] and Appel reactions[33] and the ligands of various transition metal catalysts.[34–37] The generation of phosphine oxide, however, remains the major limitation of this family of chemical reactions as stoichiometric by-products are especially inherent in the separation.[38] Although many strategies have been developed to remove phosphine oxide,[39–42] this basic problem remains. Therefore, new phosphorus-mediated reactions that convert phosphine oxides into phosphorus(V) reagents are desirable.[43]

Bis(trichloromethyl)carbonate (BTC), also known as triphosgene or solid phosgene, has been considered an easily handled alternative to highly toxic phosgene, which has been employed in chlorination, acylation, rearrangement

CONTACT Zhenhua Li lizhenhua@zjut.edu.cn College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P.R. China.
Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2020.1782910.

and cyclization.[44–48] During our continuous efforts to expand the chemistry of BTC, we developed an eco-friendly system of BTC and triphenylphosphine oxide (TPPO) which generated a versatile chlorination reagent triphenylphosphine dichloride (TPPDC), and applied it in the construction of biologically relevant heterocyclic compounds.[28,49–51] Herein, we report a convenient and efficient one-pot cascade synthesis of 2,4-dichloroquinazolines directly from isatin-3-oximes with the addition of BTC and triarylphosphine oxide.

Results and discussion

In our previous work,[28] we explored the reaction between *o*-aminobenzonitrile and the BTC/TPPO system and proposed 2-isocyanatobenzonitrile as the key intermediate. Subsequently, we hypothesized that isatin-3-oximes might replace *o*-aminobenzonitrile in completing this reaction as *o*-aminobenzonitrile could be conveniently generated from isatin-3-oximes where 2-isocyanatobenzonitriles were the intermediate during the procedure.[52,53] As a result, we chose isatin-3-oxime **1a** (1 equiv.) to perform the model reaction with the addition of BTC (2 equiv.)/TPPO (1 equiv.) at 120 °C (Table 1, entry 1). Surprisingly, we obtained a 68% yield of 2,4-dichloroquinazoline. It is reported that electron-deficient or –rich triarylphosphine oxides greatly influence TPPDC formation.[38] Thus, we began a series of optimization studies with a view to increasing the yield to more practical levels.

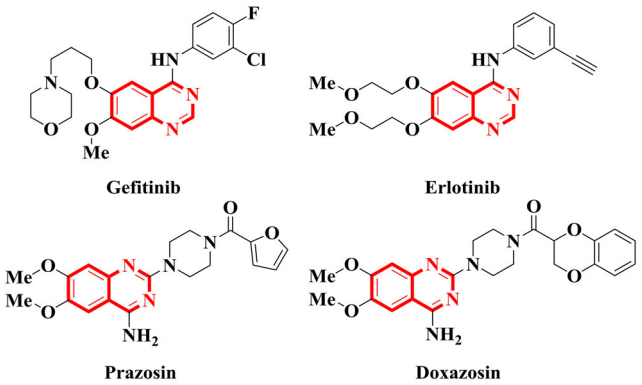


Figure 1. Current medical applications of quinazolines.

The substituents on the TPPO showed a critical effect on the reaction. As listed in Table 1, electron-withdrawing groups on the TPPO exhibited lower yields and longer reaction times (Table 1, entry 2). However, those TPPO with electron-donating groups afforded excellent yields in a short time (Table 1, entries 3, 4). There seemed to be some steric effect in this reaction because tris(1,1′-biphenyl)-4-yl)phosphine oxide (**3e**) caused a significant decline in the outcomes (Table 1, entry 5). Tri(4-methoxyphenyl)phosphine oxide (**3d**) showed better reactivity providing 2,4-dichloroquinazoline with 92% yield (Table 1, entry 4).

The reaction conditions were optimized further. The yield remained excellent when the quantity of triarylphosphine oxides decreased, although a longer reaction time was required (Table 2, entries 1–3). Remarkably, the reaction result was unsatisfactory using 0.2 equiv **3d**, which generated a moderate yield of **2a** after heating for 24 h (Table 2, entry 4). These results indicated the importance of the amount of triarylphosphine oxides. Moreover, they suggested that decreasing BTC might inhibit this transformation (Table 2, entry 5).

With the optimized conditions established, a series of isatin-3-oximes was exposed to the developed conditions, and the results are presented in Table 3. Functional groups were tolerated and the desired products **2** were afforded in moderate to excellent yields. Generally, electron-withdrawing

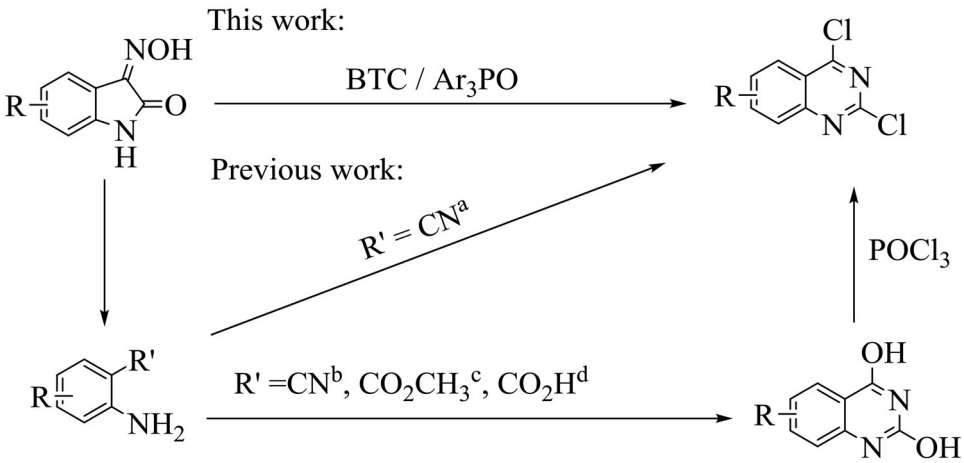
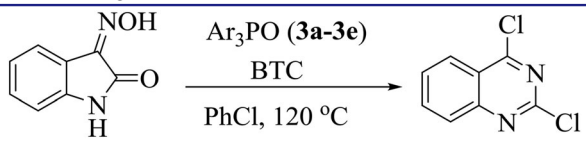


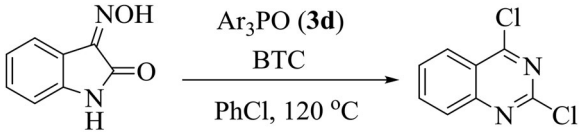
Figure 2. Synthesis of 2,4-dichloroquinazolines.

Table 1. Optimization of triarylphosphine oxides.[a]

Entry	Reagent	R (Ar = R-Ph)	Time (h)	Yield[b] (%)
				
	1a			**2a**
1	**3a**	H	2	68
2	**3b**	4-CH_3	1.5	87
3	**3c**	3,4,5-triF	3	62
4	**3d**	4-OCH_3	1	92
5	**3e**	4-Ph	4	38

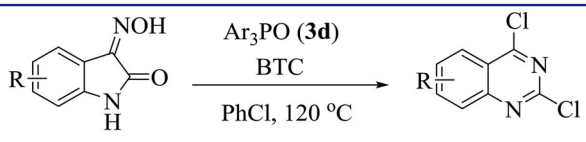
[a]Reaction conditions: **1a** (3 mmol), Ar_3PO (3 mmol), BTC (2 mmol) were used.
[b]Isolated yields based on **1a**.

Table 2. Optimization of reaction conditions.[a]

Entry	1a:BTC:**3d**	Time (h)	Yield[b] (%)
			
	1a		**2a**
1	1:2:1	1	92
2	1:2:0.5	2	92
3	1:2:0.3	3	92
4	1:2:0.2	24	60
5	1:0.7:0.3	3	75

[a]Reaction conditions: BTC in PhCl was dropped into **3d** at -5–0 °C followed by reacting at room temperature for 30 min, then **1a** was added and the temperature was increased to 120 °C.
[b]Isolated yields based on **1a**.

Table 3. Synthesis of 2,4-dichloroquinazolines 2 from isatin-3-oximes **1**.[a]

Entry	Product	R (2a–2n)	Time (h)	Yield[b] (%)
				
	1a-1n			**2a-2n**
1	**2a**	H	3	93
2	**2b**	6-OMe	3	94
3	**2c**	6-Me	3	93
4	**2d**	6,7-diOMe	4	92
5	**2e**	5,7-diMe	4	92
6	**2f**	6-Cl	4	88
7	**2g**	8-Cl	4	87
8	**2h**	7-F	6	74
9	**2i**	6-F	6	85
10	**2j**	6-Br	6	71
11	**2k**	6-NO_2	6	63
12	**2l**	5,7-Cl_2	6	66
13	**2m**	8-Br	6	71
14	**2n**	6-Cl-8-Me	6	82

[a]Reaction conditions: BTC (2.2 mmol) in PhCl was dropped into **3d** (0.9 mmol) at −50 °C followed by reacting at room temperature for 30 min, then **1a**–**1n** (3 mmol) was added and the temperature was increased to 120 °C.
[b]Isolated yields based on **1a**–**1n**.

groups (Table 3, entries 6–13) exert a greater influence than electron-donating groups (Table 3, entries 1–5). Halogen atoms are preferred at the *para*-position of the nitrogen atom (Table 3, entries 6–8), as opposed to the *meta*-position (Table 3, entries 9, 12). Different halogen atoms might have diverse effects, as the presence of bromine atoms but not chlorine atoms reinstated the reaction efficiency (Table 3, entries 6, 7 vs 10, 13). Although the nitro group was tolerated, this reaction gave the lowest yield in these experiments at 63% (Table 3, entry 11). Interestingly, when both electron-donating and -withdrawing groups substituted the isatin-3-oxime, the electron-withdrawing group played the leading role in the electronic effect (Table 3, entry 14).

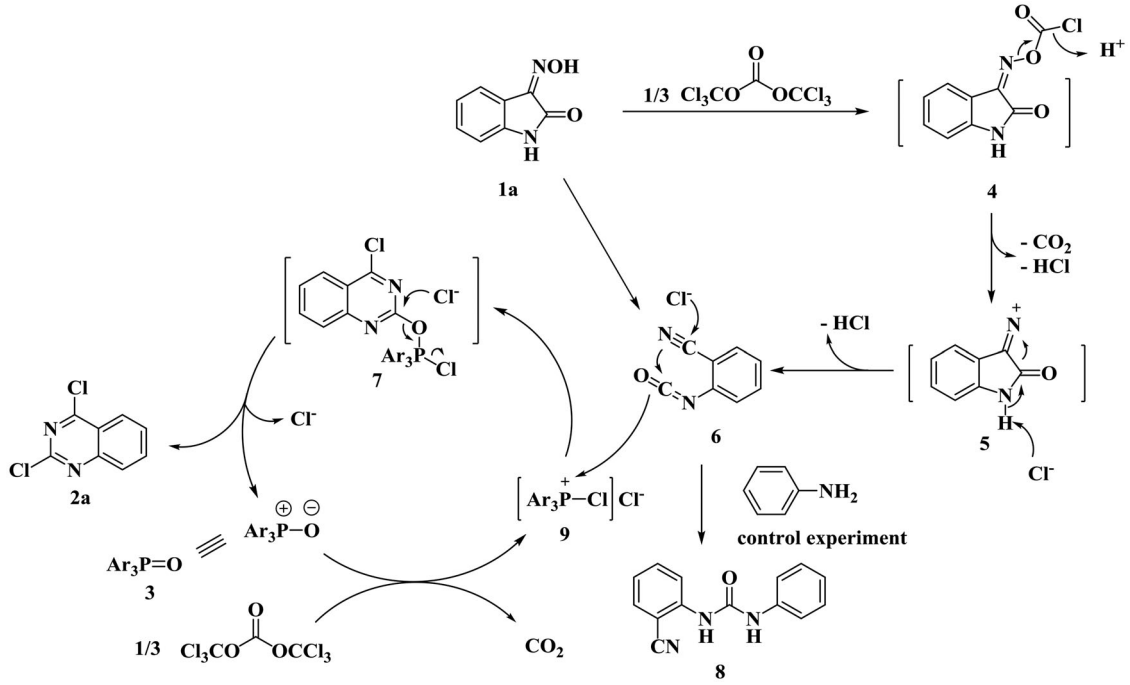
In order to demonstrate the reaction mechanism, aniline was added into the reaction mixture to capture the key intermediate **6**. 1-(2-Cyanophenyl)-3-phenylurea **8** was obtained, indicating the formation of 2-isocyanatobenzonitrile as the intermediate. On the basis of the above and the previous literature,[28,50,53,54] a plausible mechanism was proposed (Scheme 1). With the mixture of the reactant, oxime **1** reacted with BTC rapidly generating the intermediate **4**. Then, under an acidic atmosphere, decarboxylation was carried out together with the leaving of chlorine leading to intermediate **5**. Next, cleavage took place with the nucleophilic attack of the chlorine anion, and the key intermediate 2-isocyanatobenzonitrile **6** was rearranged and formed. Partially, the intermediate **6** could also be generated by simple heating of isatin-3-oxime **1**. Meanwhile with the temperature increase, BTC suffered a nucleophilic attack from triarylphosphine oxide **3** and generated chlorophosphonium salt **9** by CO_2 extrusion. The intermediate **6** was captured by the chlorophosphonium salt **9**, affording intermediate **7**. Finally, the product **2** was afforded by the S_NAr mechanism, replacing the oxygen atom by a chloride anion.

Conclusion

In summary, an efficient one-pot synthesis of 2,4-dichloroquinazolines in moderate to excellent yields from isatin-3-oximes with the addition of BTC and triarylphosphine oxide has been developed. This operationally simple protocol provides an alternative 2,4-dichloroquinazolines synthetic pathway to the classical chlorination reaction of quinazolinedones. Further efforts to extend this BTC system to the preparation of other useful heterocyclic compounds are currently underway in our laboratories.

Experimental

All reagents were purchased from commercial sources and used without further purification unless otherwise indicated. *Caution!* BTC will release phosgene in a moist environment, especially at elevated temperatures; it is highly not recommended to add BTC over 80 °C. Analytical TLC (thin-layer chromatography) was performed with 0.25 mm silica gel G with a 254 nm fluorescent indicator. Melting points (mp) were obtained on digital melting point apparatus WRS-1B and are uncorrected. ^{1}H NMR, ^{13}C NMR were recorded at VARAIN-400 on a 400 MHz and 100 MHz, respectively. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ or tetramethylsilane as the internal standard. Chemical shifts (δ) were reported as part per million in δ scale



Scheme 1. Plausible mechanism.

downfield from TMS. EI-MS were recorded on a ThermoFisher ITQ1100 Ion Trap Mass Spectrometer. Purification of products was accomplished by column chromatography on silica gel. The Supplemental Materials contains full characterization data and sample ^{1}H and ^{13}C NMR spectra of the known products (supporting information Figures S1–S32).

General procedure for the synthesis of 2,4-dichloroquinazolines (2)

BTC (0.65 g, 2.2 mmol in 6 mL of PhCl) was added to a stirred solution of tris(4-methoxyphenyl)phosphine oxide **3d** (0.33 g, 0.9 mmol in 5 mL PhCl) dropwise in a round bottom flask placed on an ice bath. After complete addition, the mixture was stirred for 30 min at room temperature. Then isatin-3-oximes **1** (3 mmol) were added, and the mixture was heated to 120 °C until completion of the reaction (followed by TLC, *n*-hexane/ethyl acetate = 10:1). After cooling, the mixture was then poured into 50 mL ice water and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified over column chromatography (*n*-hexane/ethyl acetate = 10:1) to afford the pure produce 2,4-dichloroquinazolins **2**. Tris(4-methoxyphenyl)phosphine oxide **3d** was recovered by column chromatography (*n*-hexane/ethyl acetate = 1:1).

General procedure for the synthesis of triarylphosphine oxide (3)

Magnesium splints (0.96 g, 40 mmol) and iodine were mixed under an argon atmosphere in a 100 mL dry flask. Bromobenzene derivatives (66 mmol) were dissolved in dry tetrahydrofuran (20 mL), and then a 5 mL portion was added until the reaction started. The reaction mixture was cooled to 0 °C followed by addition of the residual bromobenzene derivatives dropwise. After complete addition, the mixture was heated to refluxing for 1 h. The mixture was cooled to 0 °C again and $POCl_3$ (1.53 g, 10 mmol) was added dropwise slowly. Further refluxing was employed for 1 h, and the mixture was cooled to room temperature. After cooling down, the mixture was then poured into ice water and extracted with dichloromethane. The organic layer was washed by aqueous $NaHCO_3$, NaCl and NaOH, respectively, and then dried over anhydrous $MgSO_4$ and concentrated. The crude reaction product was recrystallized using ethanol.

ORCID

Zhenhua Li http://orcid.org/0000-0002-8092-3571

References

[1] Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent Advances in the Structural Library of Functionalized Quinazoline and Quinazolinone Scaffolds: Synthetic Approaches and Multifarious Applications. *Eur. J. Med. Chem.* **2014**, *76*, 193–244. DOI: 10.1016/j.ejmech.2014.02.005.

[2] Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. Synthetic Approaches, Functionalization and Therapeutic Potential of Quinazoline and Quinazolinone Skeletons: The Advances Continue. *Eur. J. Med. Chem.* **2015**, *90*, 124–169. DOI: 10.1016/j.ejmech.2014.10.084.

[3] Li, Y.; Xiao, J.; Zhang, Q.; Yu, W.; Liu, M.; Guo, Y.; He, J.; Liu, Y. The Association between anti-Tumor Potency and Structure-Activity of Protein-Kinases Inhibitors Based on Quinazoline Molecular Skeleton. *Bioorg. Med. Chem.* **2019**, *27*, 568–577. DOI: 10.1016/j.bmc.2018.12.032.

[4] Larroque-Lombard, A. L.; Todorova, M.; Golabi, N.; Williams, C.; Jean-Claude, B. J. Synthesis and Uptake of Fluorescence-Labeled Combi-Molecules by p-Glycoprotein-Proficient and

-Deficient Uterine Sarcoma Cells Mes-sa and Mes-sa/dx5. *J. Med. Chem.* **2010**, *53*, 2104–2113. DOI: 10.1021/jm9016043.

[5] Li, E. D.; Lin, Q.; Meng, Y. Q.; Zhang, L. Y.; Song, P. P.; Li, N.; Xin, J. C.; Yang, P.; Bao, C. N.; Zhang, D. Q.; et al. 2,4-disubstituted Quinazolines Targeting Breast Cancer Cells via Egfr-pi3k. *Eur. J. Med. Chem.* **2019**, *172*, 36–47. DOI: 10.1016/j.ejmech.2019.03.030.

[6] Smits, R. A.; Adami, M.; Istyastono, E. P.; Zuiderveld, O. P.; van Dam, C. M.; de Kanter, F. J.; Jongejan, A.; Coruzzi, G.; Leurs, R.; de Esch, I. J. Synthesis and Qsar of Quinazoline Sulfonamides as Highly Potent Human Histamine h4 Receptor Inverse Agonists. *J. Med. Chem.* **2010**, *53*, 2390–2400. DOI: 10.1021/jm901379s.

[7] Alagarsamy, V.; Chitra, K.; Saravanan, G.; Solomon, V. R.; Sulthana, M. T.; Narendhar, B. An Overview of Quinazolines: Pharmacological Significance and Recent Developments. *Eur. J. Med. Chem.* **2018**, *151*, 628–685. DOI: 10.1016/j.ejmech.2018.03.076.

[8] Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. 2,4-diamino-6,7-Dimethoxyquinazolines. 4. 2-[4-(Substituted Oxyethoxy) Piperidino] Derivatives as Alpha 1-Adrenoceptor Antagonists and Antihypertensive Agents. *J. Med. Chem.* **1988**, *31*, 516–520. DOI: 10.1021/jm00398a006.

[9] Sacher, A. G.; Komatsubara, K. M.; Oxnard, G. R. Application of Plasma Genotyping Technologies in Non-Small Cell Lung Cancer: A Practical Review. *J. Thorac. Oncol.* **2017**, *12*, 1344–1356. DOI: 10.1016/j.jtho.2017.05.022.

[10] Gass-Jegu, F.; Gschwend, A.; Gairard-Dory, A. C.; Mennecier, B.; Tebacher-Alt, M.; Gourieux, B.; Quoix, E. Gastrointestinal Perforations in Patients Treated with Erlotinib: A Report of Two Cases with Fatal Outcome and Literature Review. *Lung Cancer* **2016**, *99*, 76–78. DOI: 10.1016/j.lungcan.2016.06.012.

[11] Lepor, H. Nonoperative Management of Benign Prostatic Hyperplasia. *J. Urol.* **1989**, *141*, 1283–1289. DOI: 10.1016/S0022-5347(17)41282-1.

[12] Shaw, Y. J.; Yang, Y. T.; Garrison, J. B.; Kyprianou, N.; Chen, C. S. Pharmacological Exploitation of the alpha1-Adrenoreceptor Antagonist Doxazosin to Develop a Novel Class of Antitumor Agents That Block Intracellular Protein Kinase b/Akt Activation. *J. Med. Chem.* **2004**, *47*, 4453–4462. DOI: 10.1021/jm049752k.

[13] Van Horn, K. S.; Burda, W. N.; Fleeman, R.; Shaw, L. N.; Manetsch, R. Antibacterial Activity of a Series of n2,n4-Disubstituted Quinazoline-2,4-Diamines. *J. Med. Chem.* **2014**, *57*, 3075–3093. DOI: 10.1021/jm500039e.

[14] Duan, H.; Lee, J. W.; Moon, S. W.; Arora, D.; Li, Y.; Lim, H. Y.; Wang, W. Discovery, Synthesis, and Evaluation of 2,4-Diaminoquinazolines as a Novel Class of Pancreatic β-Cell-Protective Agents against Endoplasmic Reticulum (ER) Stress. *J. Med. Chem.* **2016**, *59*, 7783–7800. DOI: 10.1021/acs.jmedchem.6b00041.

[15] Deng, X.; Guo, L.; Xu, L.; Zhen, X.; Yu, K.; Zhao, W.; Fu, W. Discovery of Novel Potent and Selective Ligands for 5-ht2a Receptor with Quinazoline Scaffold. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3970–3974. DOI: 10.1016/j.bmcl.2015.07.030.

[16] Zhu, L.; Jin, J.; Liu, C.; Zhang, C.; Sun, Y.; Guo, Y.; Fu, D.; Chen, X.; Xu, B. Synthesis and Biological Evaluation of Novel Quinazoline-Derived Human pin1 Inhibitors. *Bioorg. Med. Chem.* **2011**, *19*, 2797–2807. DOI: 10.1016/j.bmc.2011.03.058.

[17] Liu, Z.; Ai, J.; Peng, X.; Song, Z.; Wu, K.; Zhang, J.; Yao, Q.; Chen, Y.; Ji, Y.; Yang, Y.; et al. Novel 2,4-Diarylaminopyrimidine Analogues (Daapalogues) Showing Potent c-Met/Alk Multikinase Inhibitory Activities. *ACS Med. Chem. Lett.* **2014**, *5*, 304–308. DOI: 10.1021/ml400373j.

[18] Mohamed, T.; Rao, P. P. N. 2,4-Disubstituted Quinazolines as Amyloid-β Aggregation Inhibitors with Dual Cholinesterase Inhibition and Antioxidant Properties: Development and Structure-Activity Relationship (SAR) Studies. *Eur. J. Med. Chem.* **2017**, *126*, 823–843. DOI: 10.1016/j.ejmech.2016.12.005.

[19] Maskrey, T.; Kristufek, T.; LaPorte, M.; Nyalapatla, P.; Wipf, P. A New Synthesis of Gefitinib. *Synlett* **2019**, *30*, 471–476. DOI: 10.1055/s-0037-1610375.

[20] Marugan, J. J.; Zheng, W.; Motabar, O.; Southall, N.; Goldin, E.; Westbroek, W.; Stubblefield, B. K.; Sidransky, E.; Aungst, R. A.; Lea, W. A.; et al. Evaluation of Quinazoline Analogues as Glucocerebrosidase Inhibitors with Chaperone Activity. *J. Med. Chem.* **2011**, *54*, 1033–1058. DOI: 10.1021/jm1008902.

[21] Hu, K.; Zhen, Q.; Gong, J.; Cheng, T.; Qi, L.; Shao, Y.; Chen, J. Palladium-Catalyzed Three-Component Tandem Process: One-Pot Assembly of Quinazolines. *Org. Lett.* **2018**, *20*, 3083–3087. DOI: 10.1021/acs.orglett.8b01070.

[22] Kumaraswamy, G.; Jena, N.; Sastry, M. N. V.; Kumar, B. A. An Expeditious, Practical Large Scale Synthesis of 4-Amino-2-Chloro-6,7-Dimethoxyquinazolinazoline. *Org. Prep. Proced. Int.* **2004**, *36*, 341–345. DOI: 10.1080/00304940409458676.

[23] Chichetti, S. M.; Ahearn, S. P.; Rivkin, A. A Novel Strategy for the Synthesis of Uracil Derivatives Using Bis(Pentafluorophenyl)Imidodicarbonate. *Tetrahedron Lett.* **2008**, *49*, 6081–6083. DOI: 10.1016/j.tetlet.2008.07.183.

[24] Verbeeck, S.; Herrebout, W. A.; Gulevskaya, A. V.; van der Veken, B. J.; Maes, B. U. Onsh: Optimization of Oxidative Alkylamination Reactions through Study of the Reaction Mechanism. *J. Org. Chem.* **2010**, *75*, 5126–5133. DOI: 10.1021/jo100858n.

[25] Sun, Z.; Wang, H.; Wen, K.; Li, Y.; Fan, E. Solvent-Free or Low-Solvent Large-Scale Preparation of Chloropyrimidine and Analogues. *J. Org. Chem.* **2011**, *76*, 4149–4153. DOI: 10.1021/jo2003715.

[26] Paul, K.; Sharma, A.; Luxami, V. Synthesis and In Vitro Antitumor Evaluation of Primary Amine Substituted Quinazoline Linked Benzimidazole. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 624–629. DOI: 10.1016/j.bmcl.2013.12.005.

[27] Chi, D. Y.; Lee, J. H.; Lee, B. S.; Shin, H.; Nam, D. H. Acetonitrile-Mediated Synthesis of 2,4-Dichloroquinoline from 2-Ethynyl Aniline and 2,4-Dichloroquinazoline from Anthranilonitrile. *Synlett* **2006**, *1*, 0065–0068. DOI: 10.1055/s-2005-922790.

[28] Li, Z. H.; Wu, D. L.; Zhong, W. H. Facile and Efficient Cyclization of Anthranilonitrile to 2,4-Dichloroquinazoline by Bis(Trichloromethyl) Carbonate and Catalytic Amount Triphenylphosphine Oxide. *Heterocycles* **2012**, *85*, 1417–1426. DOI: 10.3987/COM-12-12466.

[29] Ramazani, A.; Ahani, H. One-Step, Three-Component Synthesis of Dialkyl 2-(Imido-n-yl)-3-(Triphenylphosphoranylidene) Butanedioates. *Phosphorus Sulfur Silicon Relat. Elem.* **2001**, *170*, 181–185. DOI: 10.1080/10426500108040594.

[30] Ramazani, A.; Reza Kazemizadeh, A. Preparation of Stabilized Phosphorus Ylides via Multicomponent Reactions and Their Synthetic Applications. *COC* **2011**, *15*, 3986–4020. DOI: 10.2174/138527211798072412.

[31] Aghahosseini, H.; Ramazani, A.; Jalayer, N. S.; Ranjdoost, Z.; Souldozi, A.; Ślepokura, K.; Lis, T. Vinylphosphonium Salt-Mediated Reactions: A One-Pot Condensation Approach for the Highly Cis-Selective Synthesis of n-Benzoylaziridines and the Green Synthesis of 1,4,2-Dioxazoles as Two Important Classes of Heterocyclic Compounds. *Org. Lett.* **2019**, *21*, 22–26. DOI: 10.1021/acs.orglett.8b03388.

[32] Swamy, K. C.; Kumar, N. N.; Balaraman, E.; Kumar, K. V. Mitsunobu and Related Reactions: Advances and Applications. *Chem. Rev.* **2009**, *109*, 2551–2651. DOI: 10.1021/cr800278z.

[33] Appel, R. Tertiäres Phosphan/Tetrachlormethan, Ein Vielseitiges Reagens Zur Chlorierung, Dehydratisierung Und pn-Verknüpfung. *Angew. Chem.* **1975**, *87*, 863–874. DOI: 10.1002/ange.19750872403.

[34] Yu, J.; Long, J.; Yang, Y.; Wu, W.; Xue, P.; Chung, L. W.; Dong, X. Q.; Zhang, X. Iridium-Catalyzed Asymmetric Hydrogenation of Ketones with Accessible and Modular Ferrocene-Based Amino-Phosphine Acid (f-Ampha) Ligands. *Org. Lett.* **2017**, *19*, 690–693. DOI: 10.1021/acs.orglett.6b03862.

[35] Chang, M.; Li, W.; Hou, G.; Zhang, X. Iridium-Catalyzed Enantioselective Hydrogenation of Cyclic Imines. *Adv. Synth. Catal.* **2010**, *352*, 3121–3125. DOI: 10.1002/adsc.201000473.

[36] Yu, J.; Duan, M.; Wu, W.; Qi, X.; Xue, P.; Lan, Y.; Dong, X. Q.; Zhang, X. Readily Accessible and Highly Efficient Ferrocene-Based Amino-Phosphine-Alcohol (f-Amphol) Ligands for Iridium-Catalyzed Asymmetric Hydrogenation of Simple Ketones. *Chemistry* **2017**, *23*, 970–975. DOI: 10.1002/chem.201604855.

[37] Almássy, A.; Rakovský, E.; Malastová, A.; Sorádová, Z.; Šebesta, R. Synthesis of Epimer of Taniaphos Ligand. *J. Organomet. Chem.* **2016**, *805*, 130–138. DOI: 10.1016/j.jorganchem.2016.01.004.

[38] Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. Catalytic Phosphorus(v)-Mediated Nucleophilic Substitution Reactions: Development of a Catalytic Appel Reaction. *J. Org. Chem.* **2011**, *76*, 6749–6767. DOI: 10.1021/jo201085r.

[39] Relles, H. M.; Schluenz, R. W. Chemical Transformations with Regenerable, Polymer-Supported Trisubstituted Phosphine Dichlorides. Efficacious Incorporation of Phosphorus Reagents on Polymer Supports. *J. Am. Chem. Soc.* **1974**, *96*, 6469–6475. DOI: 10.1021/ja00827a034.

[40] Barrett, A. G.; Roberts, R. S.; Schroder, J. Impurity Annihilation: Chromatography-Free Parallel Mitsunobu Reactions. *Org. Lett.* **2000**, *2*, 2999–3001. DOI: 10.1021/ol006313g.

[41] Dandapani, S.; Curran, D. P. Separation-Friendly Mitsunobu Reactions: A Microcosm of Recent Developments in Separation Strategies. *Chemistry* **2004**, *10*, 3130–3138. DOI: 10.1002/chem.200400363.

[42] Cao, J. J.; Zhou, F.; Zhou, J. Improving the Atom Efficiency of the Wittig Reaction by a "Waste as Catalyst/Co-catalyst" Strategy. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 4976–4980. DOI: 10.1002/anie.201000896.

[43] Cordell, D.; Drangert, J.-O.; White, S. The Story of Phosphorus: Global Food Security and Food for Thought. *Glob.* Environ. Change **2009**, *19*, 292–305. DOI: 10.1016/j.gloenvcha.2008.10.009.

[44] Su, W.; Zhong, W.; Bian, G.; Shi, X.; Zhang, J. Recent Advances in the Chemistry of Trichloromethyl Chloroformate Andbis-(Trichloromethyl) Carbonate. *Org. Prep. Proced. Int.* **2004**, *36*, 499–547. DOI: 10.1080/00304940409355972.

[45] Su, W.; Weng, Y.; Zheng, C.; Zhang, Y.; Shi, F.; Hong, B.; Chen, Z.; Li, J.; Li, Z. Recent Developments in the Use Ofbis-(Trichloromethyl) Carbonate in Synthesis. *Org. Prep. Proced. Int.* **2009**, *41*, 93–141. DOI: 10.1080/00304940902885839.

[46] Villalpando, A.; Ayala, C. E.; Watson, C. B.; Kartika, R. Triphosgene-Amine Base Promoted Chlorination of Unactivated Aliphatic Alcohols. *J. Org. Chem.* **2013**, *78*, 3989–3996. DOI: 10.1021/jo400341n.

[47] Saputra, M. A.; Ngo, L.; Kartika, R. Synthesis of Vinyl Chlorides via Triphosgene-Pyridine Activation of Ketones. *J. Org. Chem.* **2015**, *80*, 8815–8820. DOI: 10.1021/acs.joc.5b01137.

[48] Cotarca, L.; Geller, T.; Répási, J. Bis(Trichloromethyl)Carbonate (BTC, Triphosgene): A Safer Alternative to Phosgene? *Org. Process Res. Dev.* **2017**, *21*, 1439–1446. DOI: 10.1021/acs.oprd.7b00220.

[49] Zou, Y.; Li, Z.; Su, W. Efficient Access to Benzochromeno[2,3-d]Pyrimidine Derivatives from *β*-Enamino Nitriles by Bis(Trichloromethyl) Carbonate and Triphenylphosphine Oxide. *J. Chem. Res.* **2014**, *38*, 143–146. DOI: 10.3184/174751914x13909344481573.

[50] Li, Z. H.; Jiang, Z. J.; Shao, Q. L.; Qin, J. J.; Shu, Q. F.; Lu, W. H.; Su, W. K. One-Pot Cascade Heterocyclization of *γ*- and *β*-Ketomalononitriles to 2,4-Dichloro-Substituted Pyrano[2,3-*d*]pyrimidines and Furo[2,3-*d*]pyrimidines Mediated by Triphosgene and Triphenylphosphine Oxide. *J. Org. Chem.* **2018**, *83*, 6423–6431. DOI: 10.1021/acs.joc.8b00669.

[51] Li, Z.; Zhong, W.; Wu, D.; Su, W. A Synthetic Method of 2,4-Dichloroquinazoline Derivatives. CN102584721A, 2012-07-18, **2012**.

[52] Zhang, C.; Du, Q. Y.; Chen, L. D.; Wu, W. H.; Liao, S. Y.; Yu, L. H.; Liang, X. T. Design, Synthesis and Evaluation of Novel Tacrine-Multialkoxybenzene Hybrids as Multi-targeted Compounds Against Alzheimer's Disease. *Eur. J. Med. Chem.* **2016**, *116*, 200–209. DOI: 10.1016/j.ejmech.2016.03.077.

[53] Campbell, J. B.; Davenport, T. V. Synthesis of Anthranilonitriles by Fragmentation of Isatin Oxime Triflates. *Synthetic Commun.* **1989**, *19*, 2255–2263. DOI: 10.1080/00397918908052624.

[54] Oxley, P.; Partridge, M. W.; Robson, T. D.; Short, W. F. A Convenient Preparation of *o*-Aminoaryl Cyanides. *J. Chem. Soc.* **1959**, 1631–1634. DOI: 10.1039/jr9590001613.