SCIENTIFIC LETTER 17

Edito

Ce mois de mai 2022 marque une date importante pour nous, il y a 18 ans AtlanChim Pharma réalisait sa toute première prestation ! Tout au long de ces 18 années auprès de nos clients, à travers plus de 1 400 contrats réalisés, nous avons été constamment animés avec enthousiasme par la passion de notre métier pour atteindre vos objectifs et synthétiser vos molécules. Depuis notre premier contrat, cet état d'esprit de « l'amour du travail bien fait » est notre ADN et notre travail au quotidien est et restera toujours gouverné par ces valeurs qui sont les nôtres : Expertise Scientifique, Transparence, Communication et Ecoute.

Ces 18 années ont vu, entre autres, l'agrandissement de notre laboratoire, l'acquisition de nouveaux équipements et l'équipe s'étoffer régulièrement avec l'arrivée de chimistes talentueux. Pour répondre à vos besoins de molécules, à vos interrogations sur des problèmes de réactivité chimique et sur l'isolement et la formation d'impuretés, en particulier, nous avons acquis tout au long de ces travaux une expertise unique en chimie, qui reste une Science expérimentale... Bien au-delà de notre savoir-faire initial en synthèse de molécules marquées à froid, avec plus de 250 isotopologues préparés, nous avons très largement étendu notre champ d'expertise à d'autres domaines : chimie des sucres, des colorants, des hétérocycles diverses et variés, du palladium et aussi à la manipulation de composés ioniques.

Cette liste non-exhaustive d'expertises n'a d'intérêt et de valeur pour nous que si elle est associée à une veille scientifique régulière et constante. Aussi, nous vous avons fait régulièrement partager cette veille scientifique au travers de nos Lettres, de nos Webinaires et aussi de nos Posts mensuels, qui sont maintenant bimensuels, sur la page LinkedIn d'AtlanChim Pharma intitulés « #The minute Of Chemistry ». Nous vous proposons ainsi notre nouvelle et 17ème lettre scientifique « An overview of the key routes to polysubstituted oxazoles ». Vous trouverez en conclusion l'ensemble des thématiques abordées au cours de toutes nos lettres scientifiques et nous vous invitons à nous remonter vos souhaits concernant les sujets que vous voudriez voir traiter.

Enfin, notre prochain Webinaire intitulé « *O*- et *N*-Méthylation: comment faire (et mieux) sans iodure de méthyle ? » que j'aurai le plaisir d'animer le 9 juin prochain à 15 h abordera une transformation très importante, les réactions de méthylation des alcools et des amines autres que celles employant de l'iodure de méthyle.

Bonne lecture !

Jacques Lebreton

Editorial

This month of May 2022 is an important date for us: 18 years ago, AtlanChim Pharma performed its very first synthesis ! Throughout these 18 years with our customers and through more than 1,400 contracts carried out, we have been constantly driven by the passion for our profession to achieve your objectives and synthesize your molecules. Since our first contract, this state of mind of « love for a job well done » has been our DNA and our daily work is and will always be governed by our values: Scientific Expertise, Transparency, Communication and Attentiveness.

These 18 years have seen, among other things, the expansion of our laboratory, the acquisition of new equipments and the team growing steadily with the arrival of talented chemists. To meet your needs for molecules, your questions about problems of chemical reactivity and the isolation and formation mechanism of impurities, in particular, we have acquired throughout this work a unique expertise in chemistry, which remains an experimental science…Well beyond our initial know-how in the synthesis of labeled molecules, with more than 250 prepared isotopologues, we have greatly extended our field of expertise to: carbohydrates chemistry, dyes, various heterocycles, palladium and also to the handling of ionic compounds.

This non-exhaustive list of expertise is only of interest and value to us if it is associated with regular and constant scientific monitoring. Also, we have regularly shared this scientific monitoring with you through our Letters, our Webinars and also our monthly Posts which are now bimonthly, on the LinkedIn of AtlanChim Pharma entitled « #The Minute Of Chemistry ». We thus offer you our new and 17th scientific letter « An overview of the key routes to polysubstituted oxazoles ». You will find in conclusion all the themes covered in our scientific letters and feel free to send us your wishes regarding the subjects you would like to see covered.

Finally, our next Webinar entitled « *O*- and *N*- Methylation: how to do (and better) without methyl iodide ? » that I will have the pleasure of hosting on 9th June at 3pm, will speak about a very important transformation, the methylation reactions of alcohols and amines other than those using methyl iodide.

Enjoy the reading!

Jacques Lebreton

An overview of the key routes to polysubstituted oxazoles

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Oxazoles are an important class of heterocycles found in a large number of natural products exhibiting a broad spectrum of biological properties.[1] Not surprisingly, oxazoles are privileged moieties present in various drugs, as well as in agrochemicals and fluorescent dyes.[2] Oxazoles are also found in a number of building blocks used as versatile synthetic intermediates.[3] Numerous synthetic methods have been published to direct and efficient regioselective preparation of polysubstituted oxazoles from readily available starting materials.[4,5]

This new *AtlanChim Pharma Scientific Letter* provides an overview on the synthetic routes for the preparation of oxazoles highlighted through recent examples in Medicinal Chemistry.

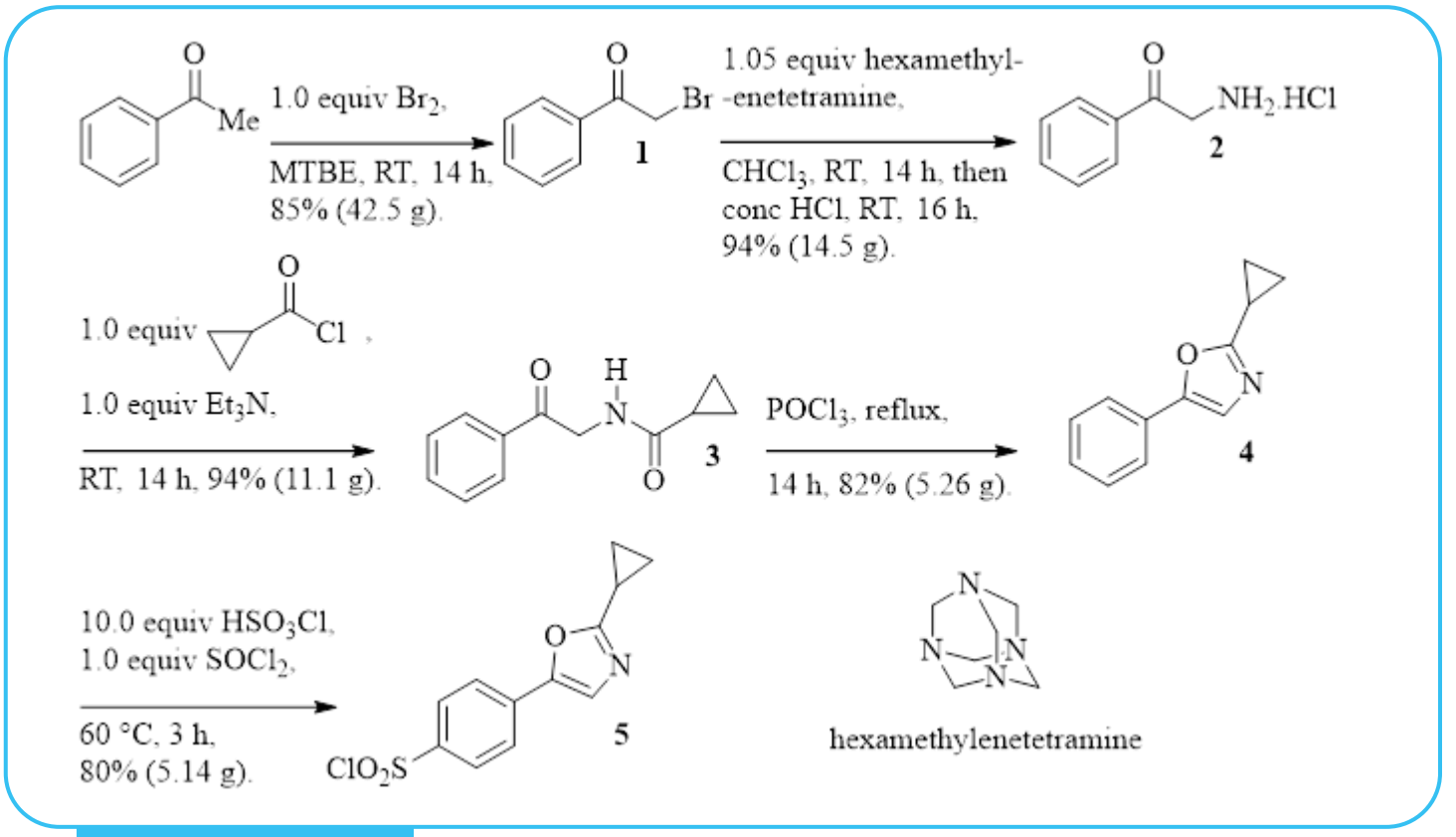
Robinson-Gabriel oxazoles synthesis

One of the oldest preparation of oxazoles is the Robinson-Gabriel synthesis in which a α-acylamino-ketone intermediate is submitted to an intramolecular cyclodehydration process. Various cyclodehydrating agents have been used such as phosphorus pentachloride, phosphorus oxychloride, polyphosphoric acid or trifluoroacetic anhydride. It should be pointed out that in 1993, Wipf published a new protocol with triphenylphosphine and iodine in the presence of triethylamine, permitting to perform this cyclocondensation under milder conditions.[6]

The efficiency of the Robinson-Gabriel oxazoles synthesis is illustrated in Scheme 1 through the preparation of the benzenesulfonyl chloride **5**, a key intermediate for the preparation of a library of novel 1,3-oxazole sulfonamide derivatives as potential tubulin polymerization inhibitors.[7] Bromination of acetophenone provided the corresponding α-bromoketone **1** which was treated with hexamethylenetetramine, then the resulting α-acylamino ketone **2** was reacted with the cyclopropylcarbonyl chloride to give the α-acylamino-ketone **3** in 75% overall yield on 10 gram scale. This latter amide **3** was involved in a Robinson-Gabriel

[1] D. X. Duc, N. T. Chung, *Curr. Org. Chem*. **2021,** *25*, 1755-1782 and cited literature.
[2] M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, *7*, 442-495 and cited literature.
[3] V. S. Brovarets *et al.*, *Eur. J. Org. Chem*. **2021**, 6511-6523 and cited literature.
[4] K. Neha, Kumari, F. Ali, K. Haider, S. Khasimbi, S. Wakode, *Synthetic Commun*. **2021**, *51*, 3501-3519 and cited literature.
[5] V. Facchinetti, C. R. B. Gomes, M. V. N. de Souza, *Tetrahedron* **2021**, *102*, 132544 and cited literature.
[6] P. Wipf, C. P. Miller, *J. Org. Chem*. **1993**, *58*, 3604-3606.
[7] E. Sisco, K. L. Barnes, *ACS Med. Chem. Lett*. **2021**, *12*, 1030-1037.

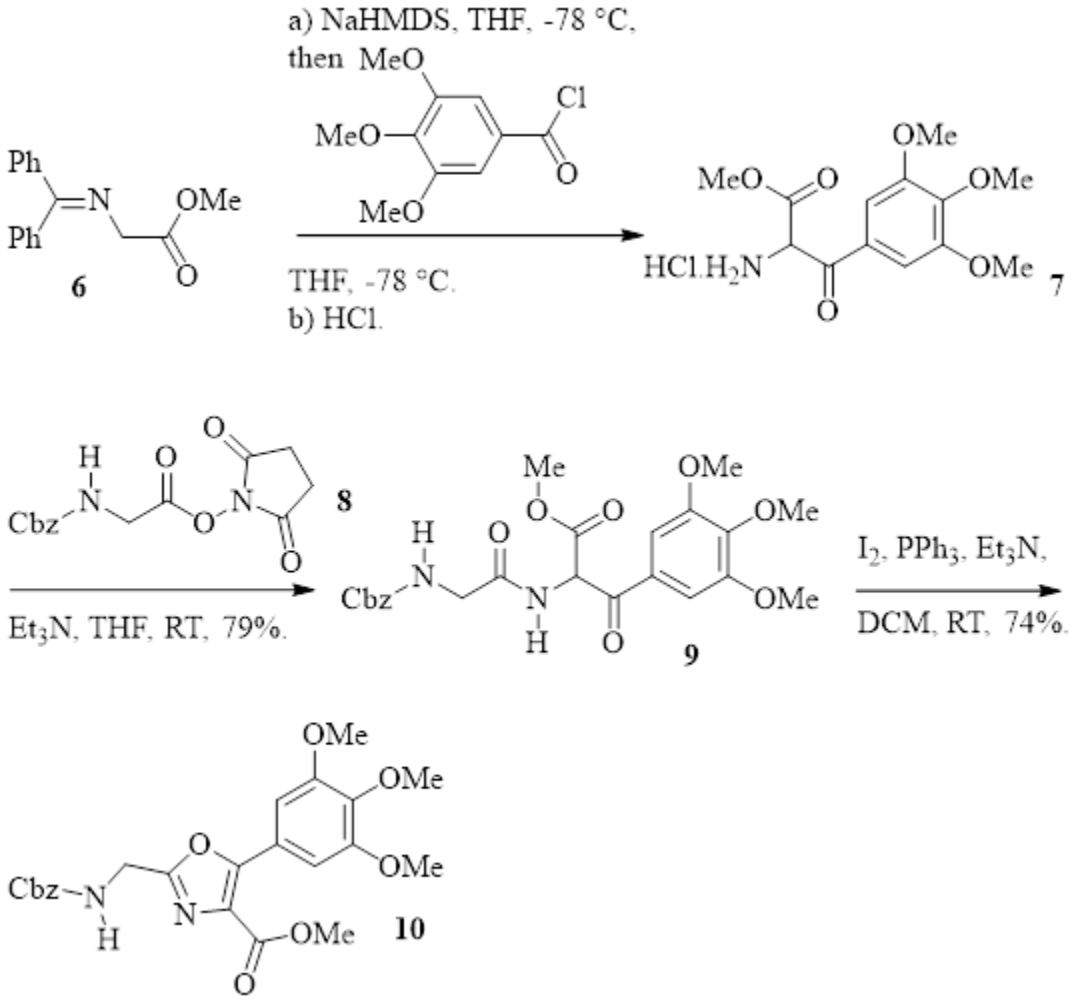
cyclodehydration with phosphorus oxychloride to afford the desired 1,3-oxazole **4** in 82% yield on 5 gram scale, and finally exposure to chlorosulfonic acid and thionyl chloride yielded the pivotal benzenesulfonyl chloride **5** in good yield. The conversion alkyl halides into primary amines with hexamethylenetetramine is known as Delépine Reaction.[8]



SCHEME 1

In the context of the preparation of oxazole based dipeptidomimetic analogues, Heck *and Coll*. used with success the Wipf's procedure as outlined in Scheme 2.[9] Deprotonation of benzophenone imine **6** with NaHMDS followed by condensation of the resulting anion with 3,4,5-trimethoxybenzoyl chloride and subsequent acid treatment with aqueous HCl afforded the crude amine **7** as hydrochloride salt. This latter crude material **7** was directly engaged in a peptide coupling reaction with activated Cbz-protected glycine **8** to provide after purification the targeted α-amido-β-ketoester intermediate **9** in 79% overall yield. Cyclodehydration of this α-amido-β-ketoester **9** using triphenylphosphine in the presence of iodine and triethylamine in dichloromethane at room temperature afforded the trisubstituted oxazole **10** in 74% yield.

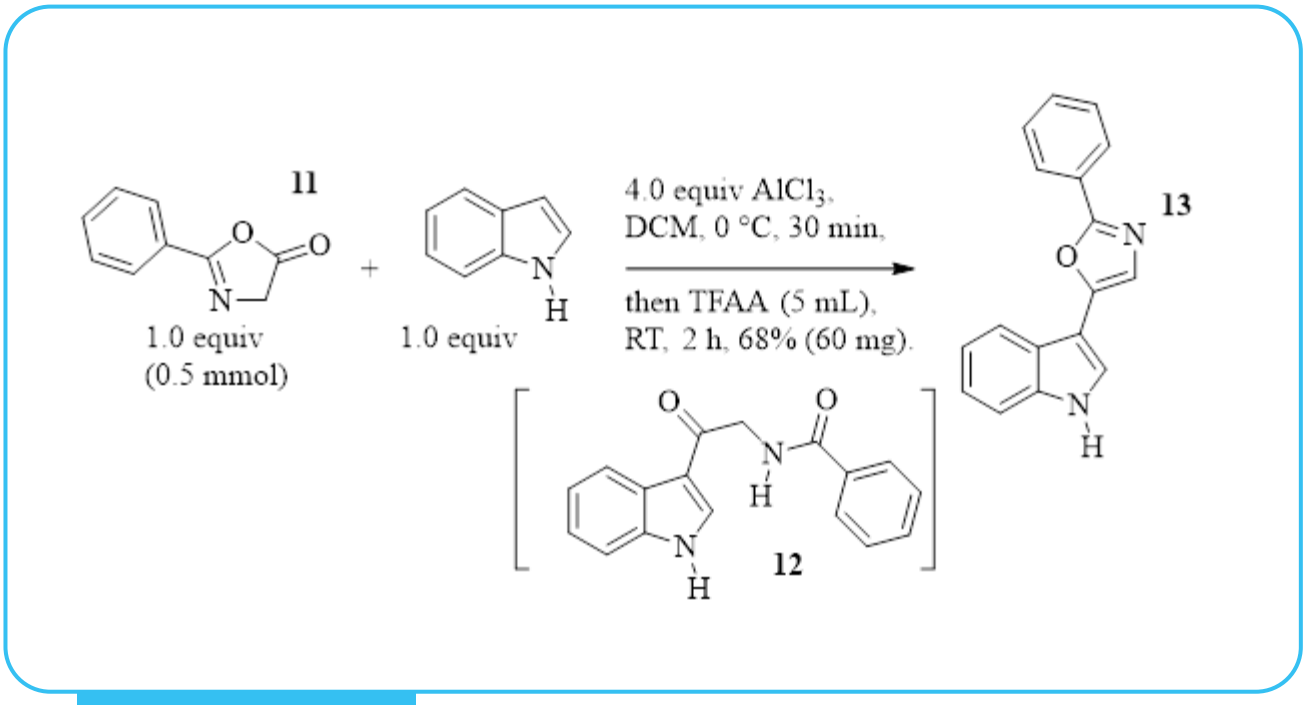
[8] M. Delépine, *Bull. Soc. Chim. Fr.* **1895**, *13*, S. 352-361.
[9] S. R. Chowdhury, P. S. Chauhan, L. M. Dedkova, X. Bai, S. Chen, P. Talukder, S. M. Hecht, *Biochemistry* **2016**, *55*, 2427-2440.



SCHEME 2

As an extension, Teppe *and Coll*. reported a one-pot substituted synthesis of oxazoles using a Friedel-Crafts/ Robinson-Gabriel sequence as presented in Scheme 3, in the context of the total synthesis of Breitfussins C, G, and H.[10] Treatment of indole with 2-phenyloxazol-5-one **11** in the presence of $AlCl_3$ in dichloromethane led to the *in situ* formation of the indole-keto-amide adduct **12**, then addition of large excess of trifluoroacetic acid anhydride (TFAA) promoted the cyclodehydration process leading to the formation of the oxazole **13** in 68% yield after purification.

[10] E. Savelson, J. J. Tepe, *J. Org. Chem. in press* (https://doi.org/10.1021/acs.joc.2c00033).

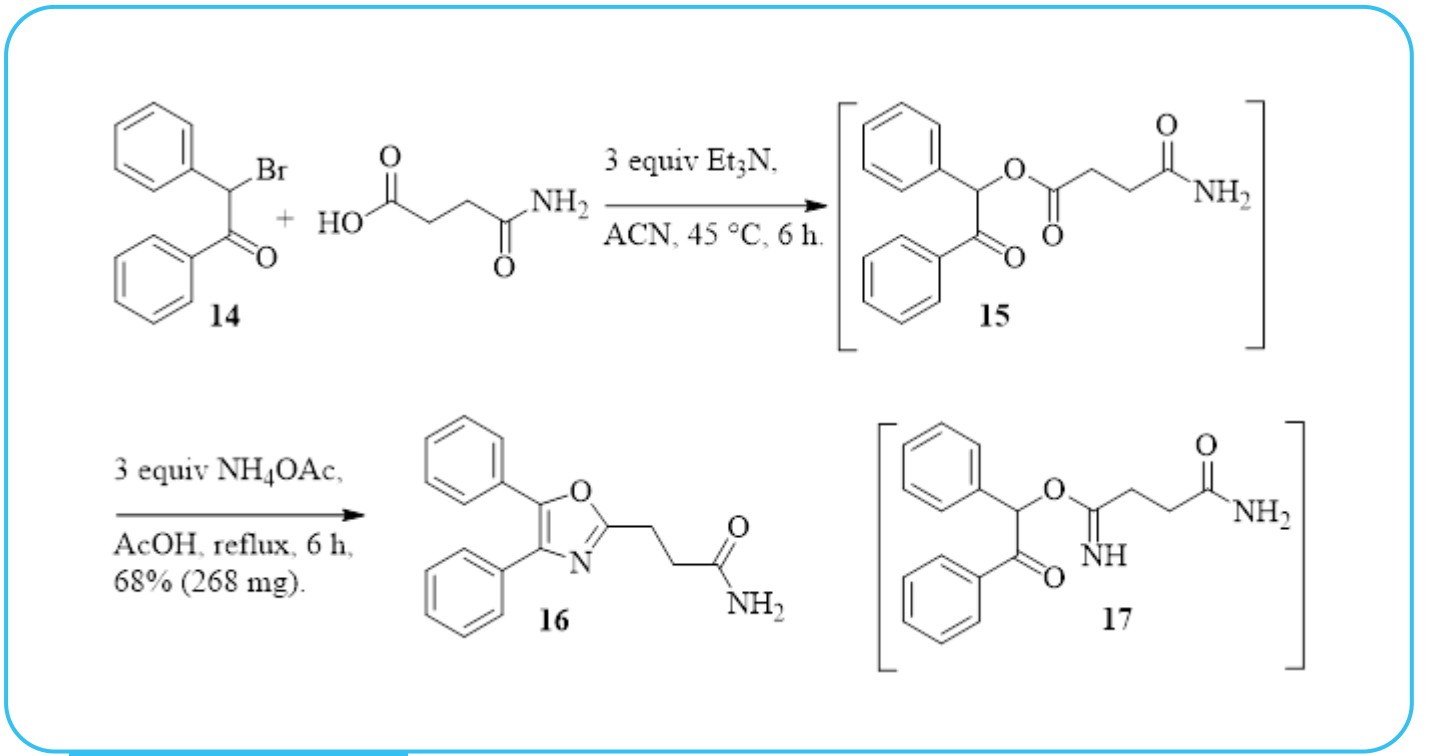


SCHEME 3

Davidson oxazole synthesis

Davidson oxazole synthesis involved the cyclization of a α-acyloxyketone intermediate in the presence of ammonium acetate, in refluxing acetic acid *via* the formation of an imidate intermediate **17**, as outlined in Scheme 4.[11] The amide derivative **16** of Oxaprozin (a nonsteroidal anti-inflammatory drug, also known as oxaprozinum) was prepared by condensation of α-bromodeoxybenzoin **14** and succinamic acid in the presence of triethylamine to afford the corresponding α-acyloxy ketone **15** which was then refluxed in acetic acid containing an excess of ammonium acetate to give the Oxaprozin analogue **16** in 68% overall yield.

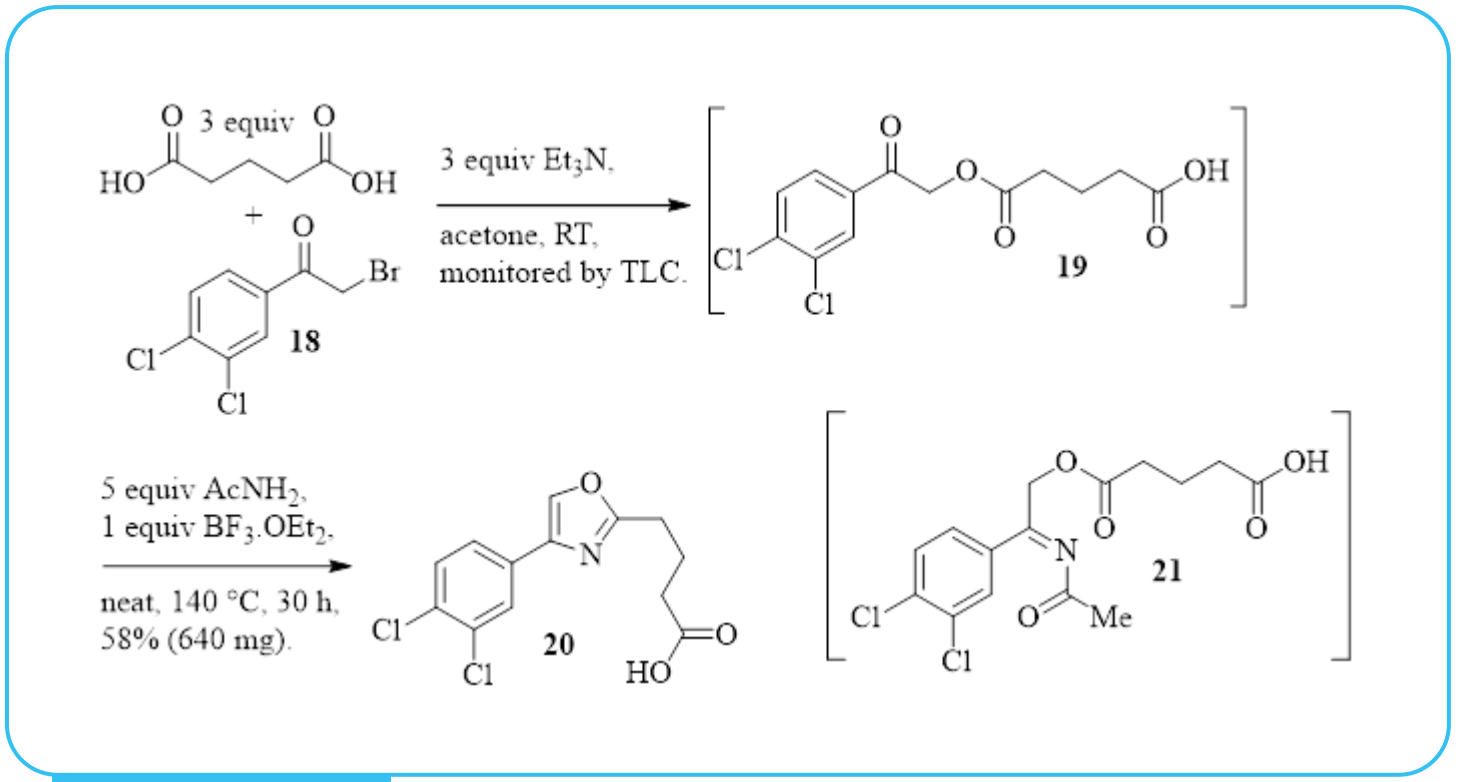
[11] E. Proschak *et al*., *J. Med. Chem.* **2019**, *62*, 8443-8460.



SCHEME 4

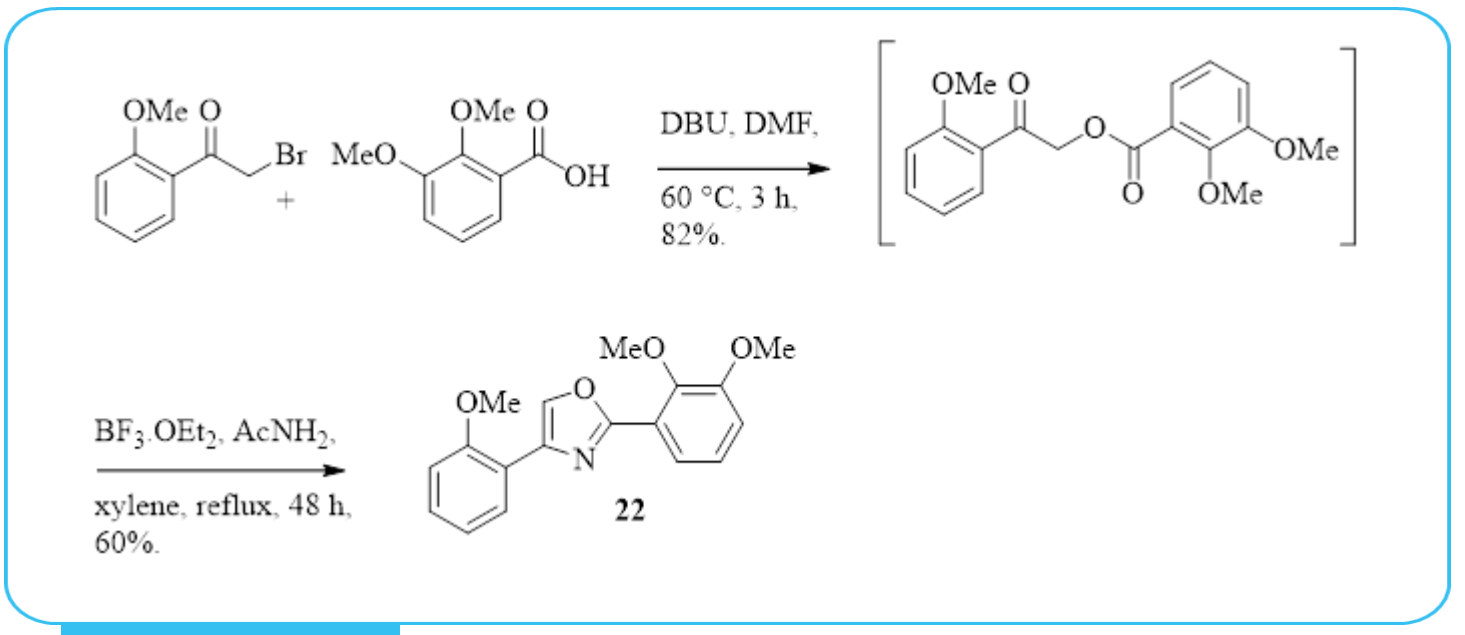
During these investigations, the authors used an improved procedure with acetamide instead of ammonium acetate, as reported in Scheme 5. The α-acyloxy ketone **19**, prepared by treatment of the α-bromoacetophenone derivative **18** with glutaric acid, was heated in acetamide as a solvent, in the presence of $BF_3.OEt_2$ to give the dichloro-analogue of Oxaprozin **20** in 58% overall yield. It was postulated that in the presence of acetamide, $BF_3.OEt_2$ catalyzed the conversion of the ketone into the *N*-acetylimine intermediate **21** which by intramolecular cyclization followed by elimination of acetic acid led to the formation of the oxazole core.[12]

[12] W. Huang, J. Pei, B. Chen, W. Pei, X. Ye, *Tetrahedron* **1996**, *52*, 10131-10136**.**



SCHEME 5

This procedure was used for the preparation of compound **22** (see Scheme 6) a derivate of naturally occurring 2,5-diphenyloxazoles isolated from the roots of *Oxytropis lanata* and showing trypanocidal activity against *Trypanosoma congolense*.[13]

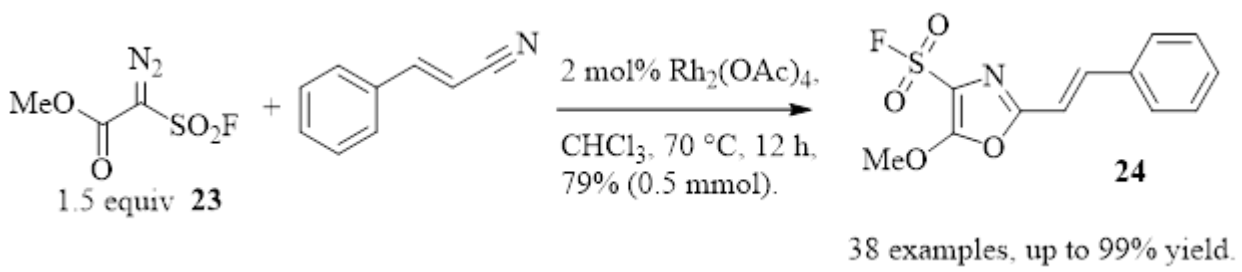


SCHEME 6

[13] K. Narita, K. Suganuma, T. Murata, R. Kondo, H. Satoh, K. Watanabe, K. Sasaki, N. Inoue, Y. Yoshimura, *Bioorg. Med. Chem.* **2021**, *42*, 116253.

Rhodium(II) chemistry

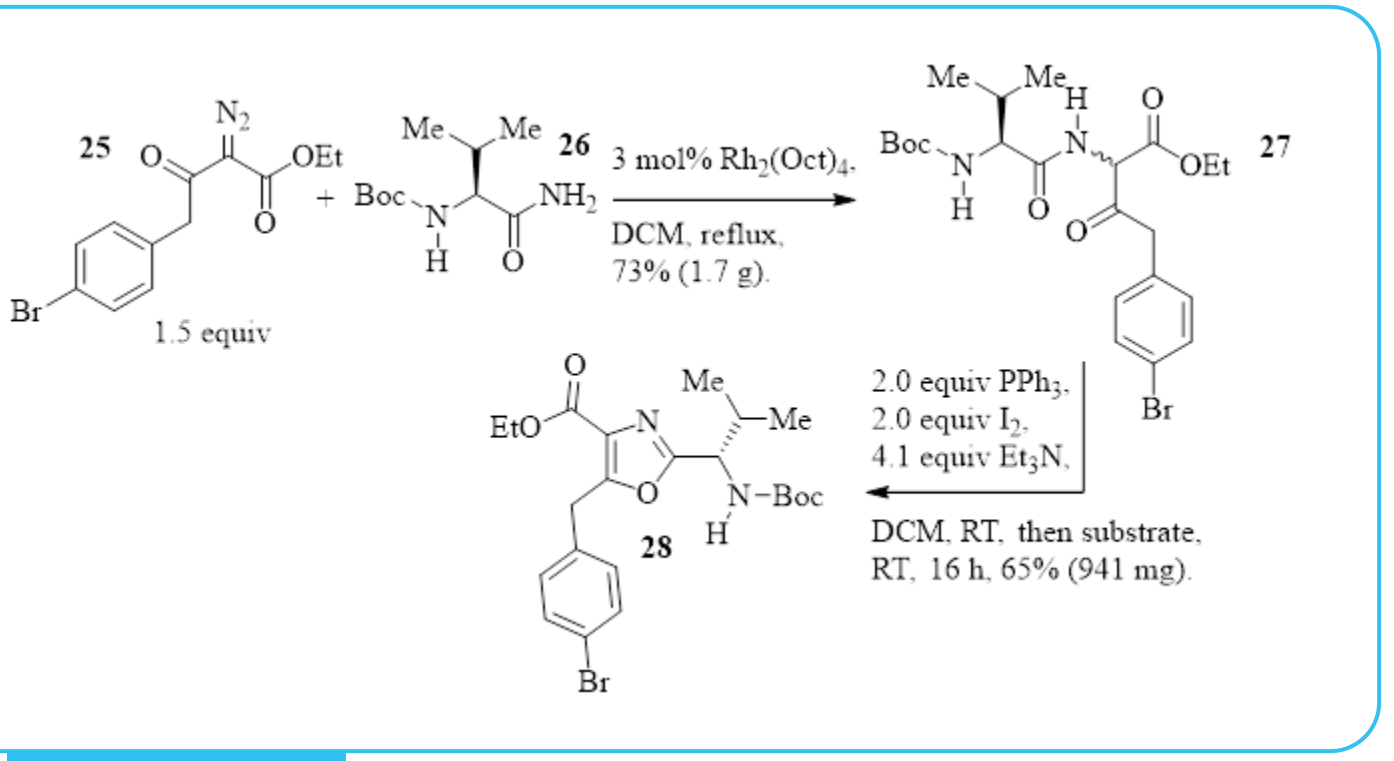
Since the pioneering investigations of Helquist in 1986 on Rh(II)-catalyzed reaction of dimethyl diazomalonate with a wide range of nitriles to provide the corresponding 4-carbomethoxy-5-methoxy-l,3-oxazoles, this transition metal mediated transformation has been largely explored.[14] Recently, a library of oxazolyl sulfonyl fluoride scaffolds, such as **24**, has been prepared by $Rh_2(OAc)_4$-catalyzed annulation of methyl-2-diazo-2-(fluorosulfonyl)acetate **23** or its corresponding ethyl ester derivative with a large variety of aryl and alkyl nitriles, as presented in Scheme 7.[15] It should be pointed out that this Rh(II)-catalyzed reaction of diazo compounds with nitriles presumably involves the 1,3-dipolar cycloaddition of the carbonylcarbene to the nitrile or the formation of a nitrile ylide intermediate followed by subsequent 1,5-cyclization.[16]



SCHEME 7

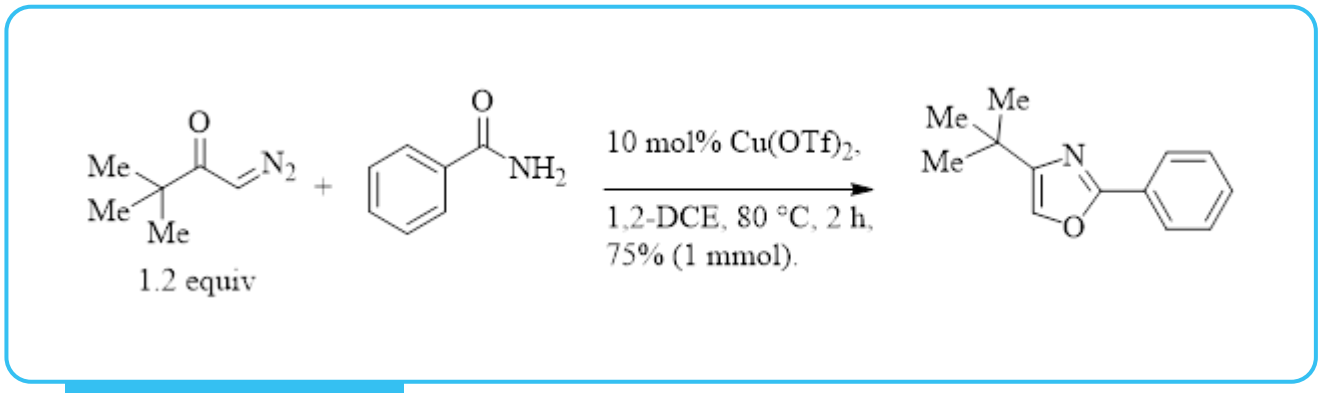
It is noteworthy that Moody *and Coll*. have extensively explored this Rh(II)-catalyzed reaction of diazo compounds with nitriles, or with carboxamides (which in this case requires a second step to promote the cyclodehydration of the α-amido-β-ketoester intermediate, *vide supra*), in an elegant way in various total synthesis of complex natural products.[17] In the course of the total synthesis of Diazonamide A, a marine secondary metabolite, the preparation of the indole *bis*-oxazole core was investigated.[18] As reported in Scheme 8, the α-diazo-β-ketoester **25** underwent rhodium(II)-catalyzed reaction with *N*-Boc-valinamide **26** resulting in N-H insertion of the intermediate rhodium carbene to provide ketoamide **27** in 73% yield. This latter α-amido-β-ketoester **27** was submitted to the Wipf's cyclodehydration protocol to give the desired trisubstituted oxazole **28** in 65% yield.

[14] R. D. Connell, F. Scavo, P. Helquist, B. Akermark, *Tetrahedron Lett*. **1986**, *27*, 5559-5562.
[15] W.-Y. Fang, S.-M. Wang, Z.-W. Zhang, H.-L. Quin, *Org. Lett.* **2020**, *22*, 8904-8909.
[16] K. J. Doyle, C. J. Moody, *Tetrahedron* **1994**, *50*, 3161-3772.
[17] J. Linder, C. J. Moody, *Chem. Commun*. **2007**, 1508-1509.
[18] J. R. Davies, P. D. Kane, C. J. Moody, *J. Org. Chem*. **2005**, *70*, 7305-7316.



SCHEME 8

More recently, Reddy *and Coll.* published a direct $Cu(OTf)_2$-catalyzed synthesis of 2,4-disubstituted oxazoles from terminal diazocarbonyl compounds and amides as presented in Scheme 9.[19] In sharp contrast with rhodium chemistry, the copper carbene intermediate attacks the carbonyl group, leading to corresponding ylide, instead of the nitrogen atom to promote the N-H insertion, then subsequent protodemetalation and cyclodehydration furnished the desired oxazole.

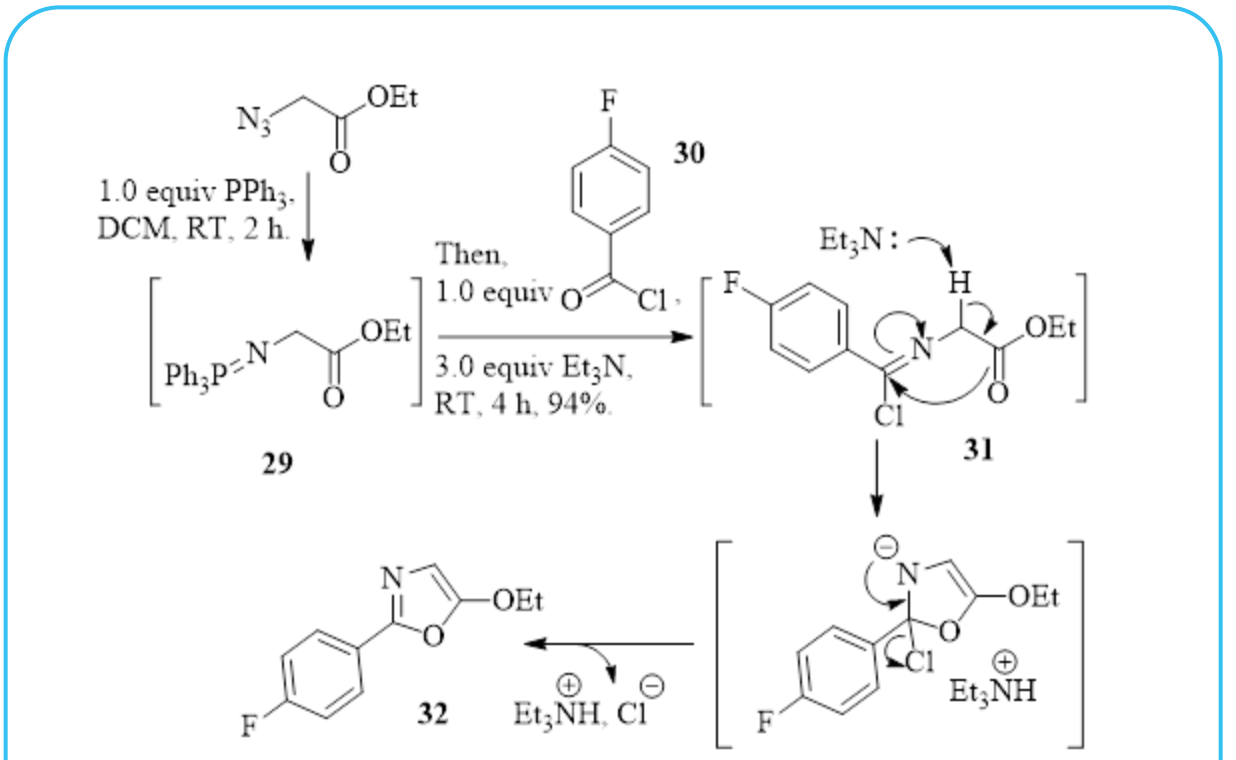


SCHEME 9

[19] B. V. Subba Reddy *et al*., *Synthesis* **2015**, *47*, 3315-3320.

Aza-Wittig reaction

Iminophosphoranes, easily accessible from azides by treatment with triphenylphosphine, undergo reaction with carbonyl compounds to form carbon-nitrogen double bond through intra- or intermolecular processes. This formation of carbon-nitrogen double bond under mild and neutral reaction conditions is known as aza-Wittig reaction, and has been largely used for the synthesis of nitrogen-containing heterocyclic compounds.[20] As reported in Scheme 10, aza-Wittig reaction of the iminophosphorane **29** with acyl chloride **30** provided the imidoyl chloride intermediate **31**, which underwent ring closure across the ester carbonyl oxygen promoted by triethylamine to give the corresponding 5-ethoxyoxazole derivative **32**.[21]



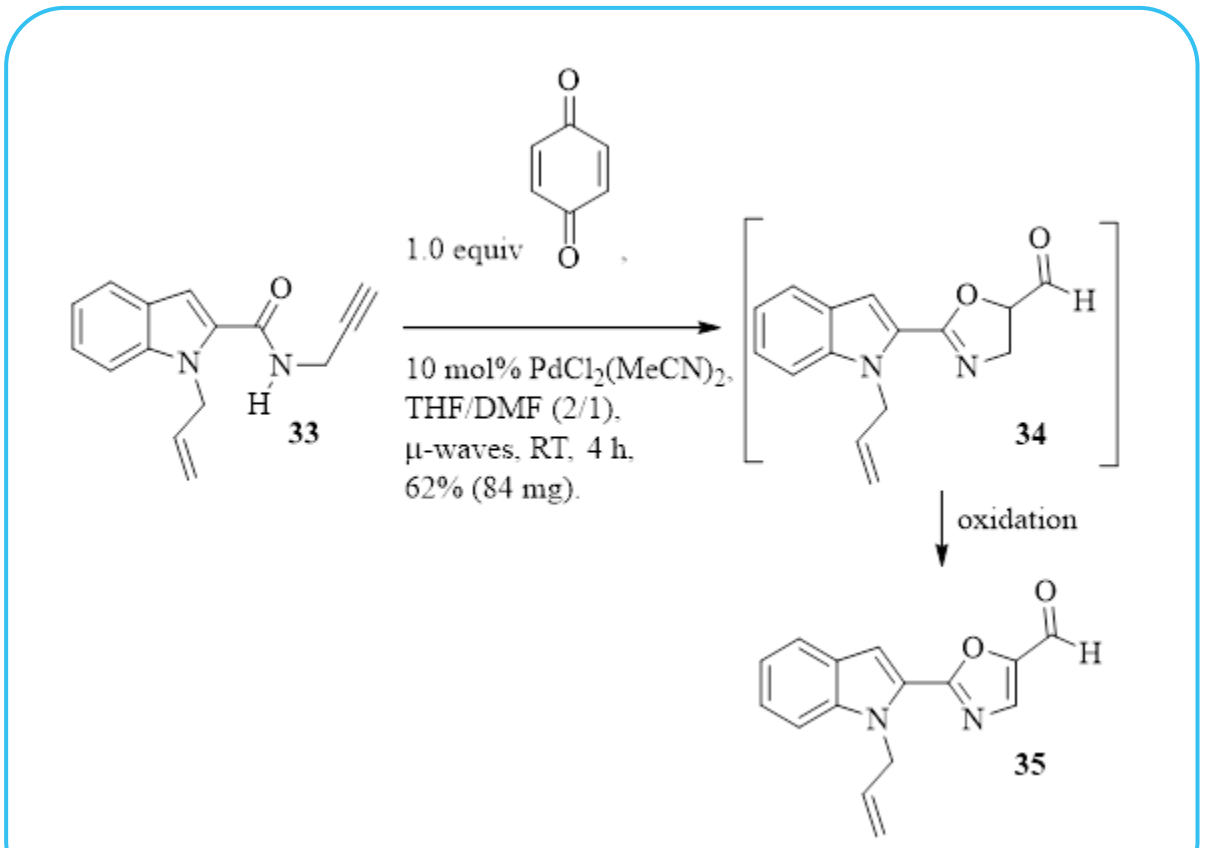
SCHEME 10

[20] P. M. Fresneda, P. Molina, *Synlett* **2004**, 1-17.
[21] N.-Y. Huang, Y.-B. Nie, M.-W. Ding, *Synlett* **2009**, 611-614.

Chemistry of the *N*-propargylamides

Metal-catalyzed or base-promoted cycloisomerization of *N*-propargylamides provided a simple access to oxazole derivatives as presented in the following examples.

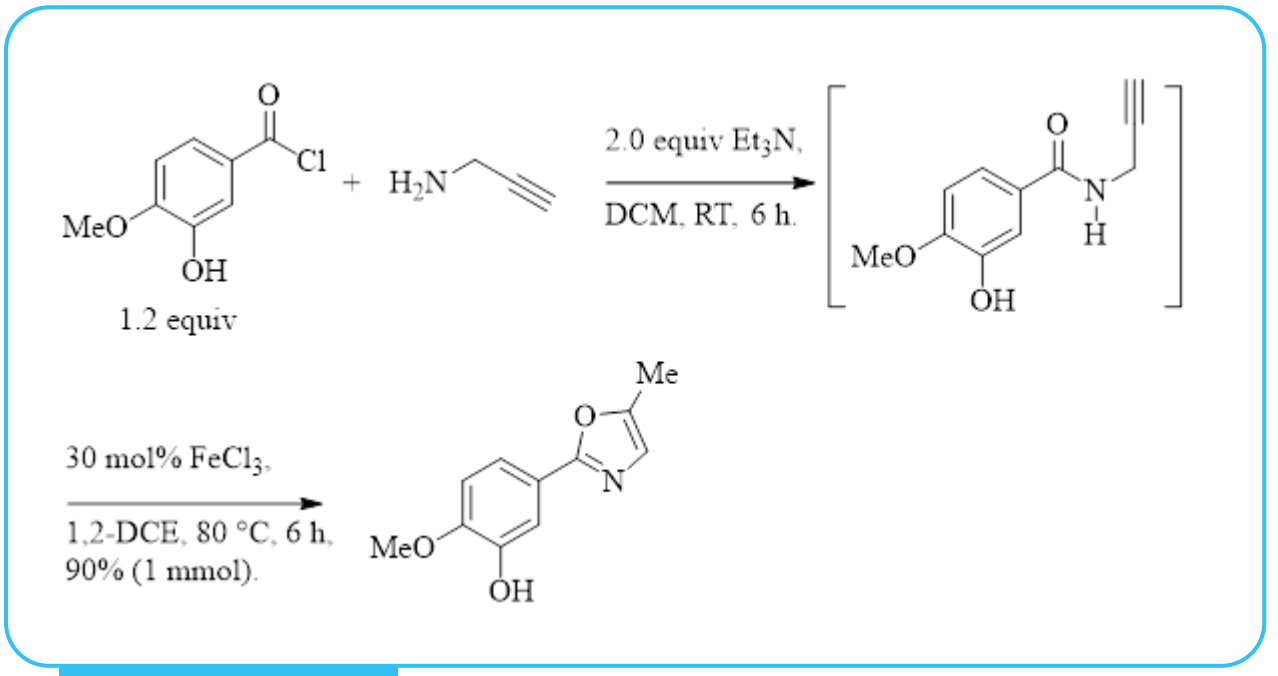
Intramolecular Pd(II)-catalyzed 5-*exodig* cyclization of the of *N*-propargylamide **33** with a catalytic amount of $PdCl_2(MeCN)_2$ and 1,4-benzoquinone to reoxidize the Pd(0) species and the 4,5-dihydrooxazole-5-carbaldehyde intermediate **34**, is a direct and efficient procedure to obtain 5-oxazolecarbaldehydes, such as **35**, as presented in Scheme 11.[22]



SCHEME 11

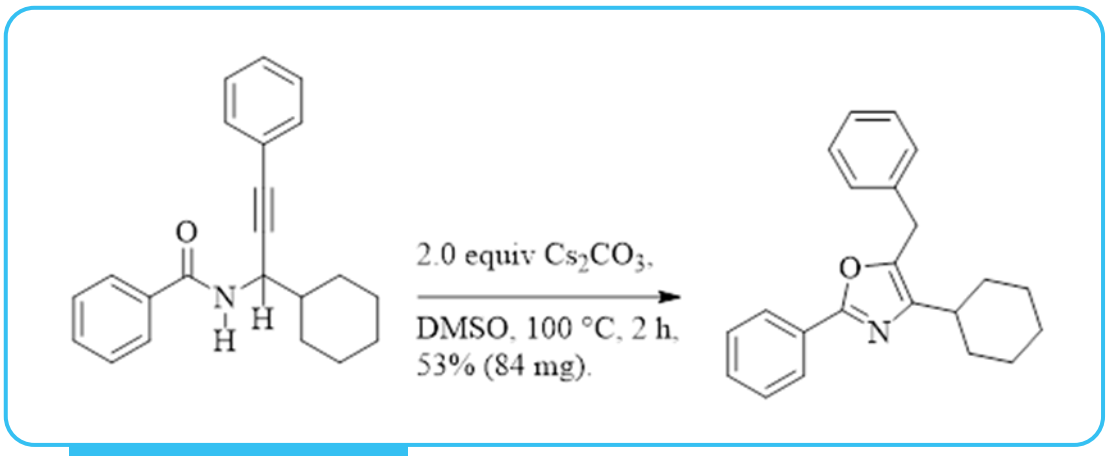
[22] E. M. Beccalli, E. Borsini, G. Broggini, G. Palmisano, S. Sottocornola, *J. Org. Chem*. **2008**, *73*, 4746-4749.

More recently, a convenient synthesis of oxazoles from *N*-propargylamides mediated by $FeCl_3$ has been published (see Scheme 12).[23] It is noteworthy that *N*-propargylamides were prepared by mixing their corresponding propargylamines and acyl chlorides in the presence of triethylamine in DCM, and the resulting solution was directly treated with $FeCl_3$ in solution in 1,2-DCE.



SCHEME 12

In 2018, a Cs_2CO_3-promoted cycloisomerization of *N*-propargylamides has been published as presented in Scheme 13.[24] A DFT investigation showed that this transformation proceeded through a sequence involving allene formation, intramolecular cyclization, and double-bond isomerization.

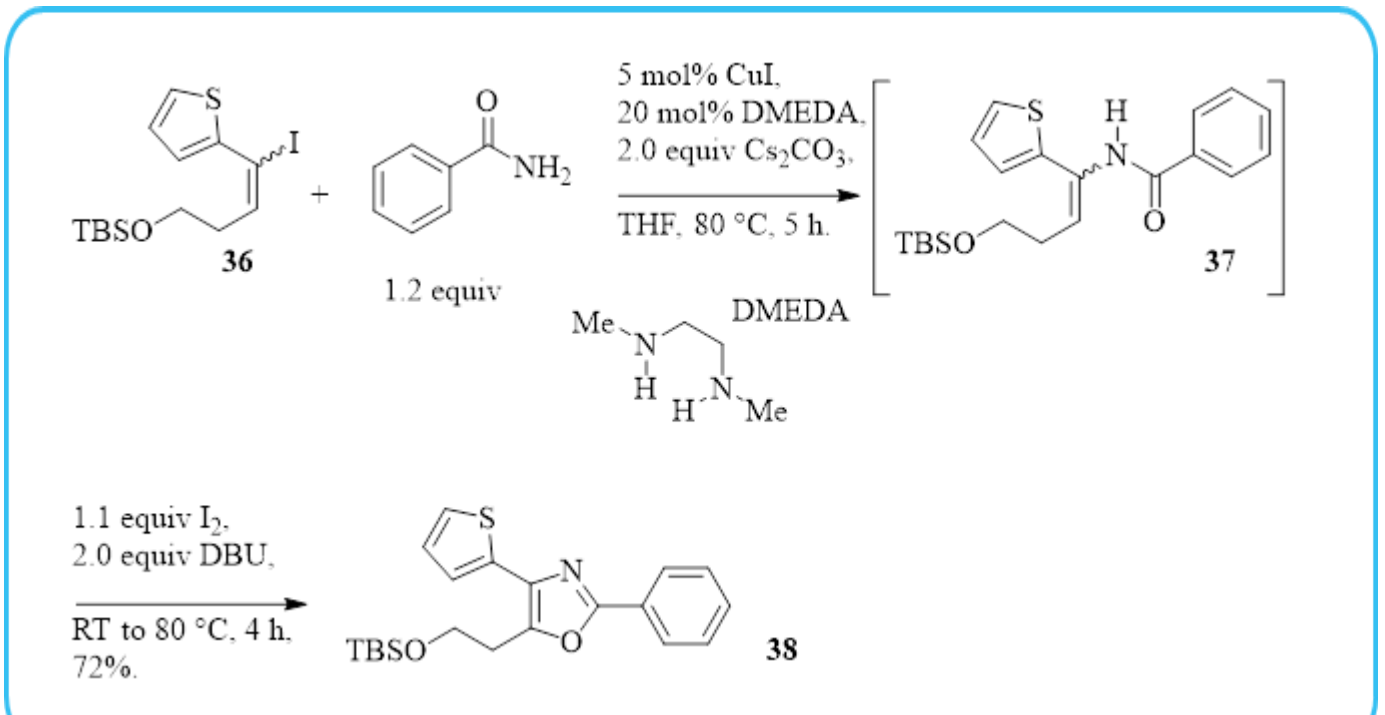


SCHEME 13

[23] G. C. Senadi, W.-P. Hu, J.-S. Hsiao, J. K. Vandavasi, C.-Y. Chen, J.-J. Wang, *Org. Lett.* **2012**, *14*, 4478-4481.
[24] L. Ahang, K. Xiao, Y. Qiao, X. Li, C. Song, J. Chang, *Eur. J. Org. Chem.* **2018**, 6913-6918.

Chemistry of the enamides

Starting from vinyl iodides and amides, Buchwald published a sequential Cu(I)-catalyzed vinylation-cyclization sequence to prepare trisubstituted oxazoles as reported in Scheme 14.[25] Cu(I)-catalyzed amidification of vinyl iodide **36** with benzamide provided the corresponding enamide **37** which was directly submitted to intramolecular cyclization promoted by iodine to yield trisubstituted oxazole **38**. It should be pointed out that this process is compatible with substrates bearing a variety of functional groups.

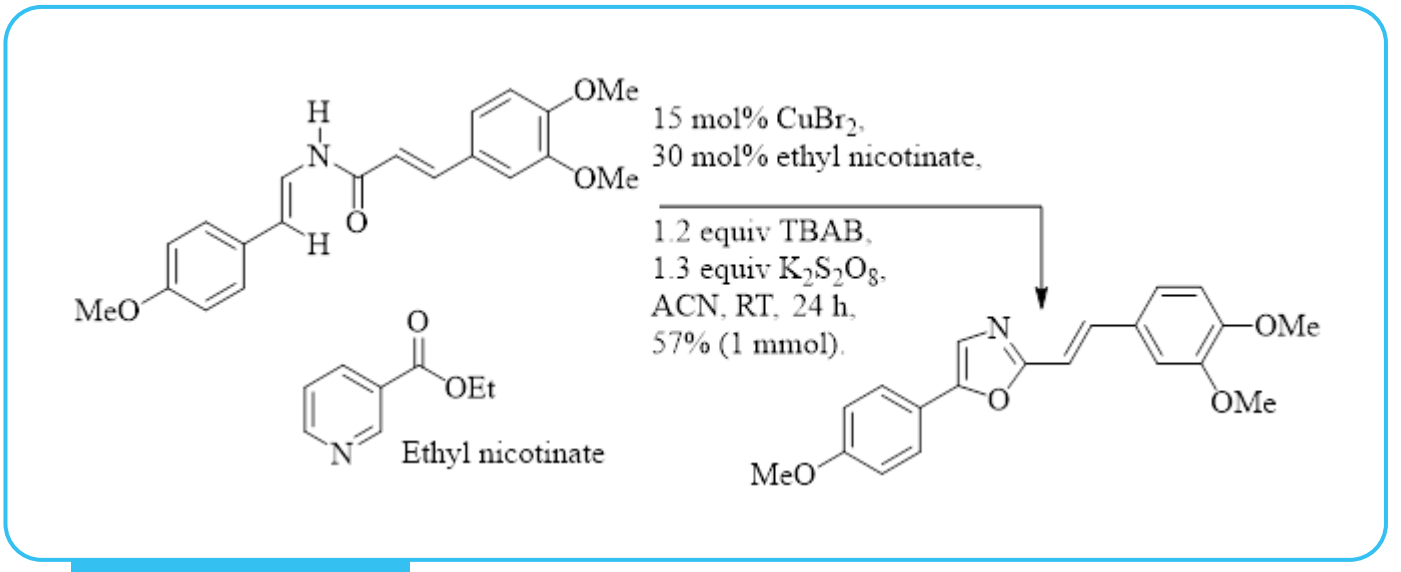


SCHEME 14

Complementary to this latter iodine-mediated cyclization of enamides, Buchwald reported a Cu(II)-catalyzed oxidative cyclization involving a vinylic C-H bond functionalization at room temperature, as described in Scheme 15.[26]

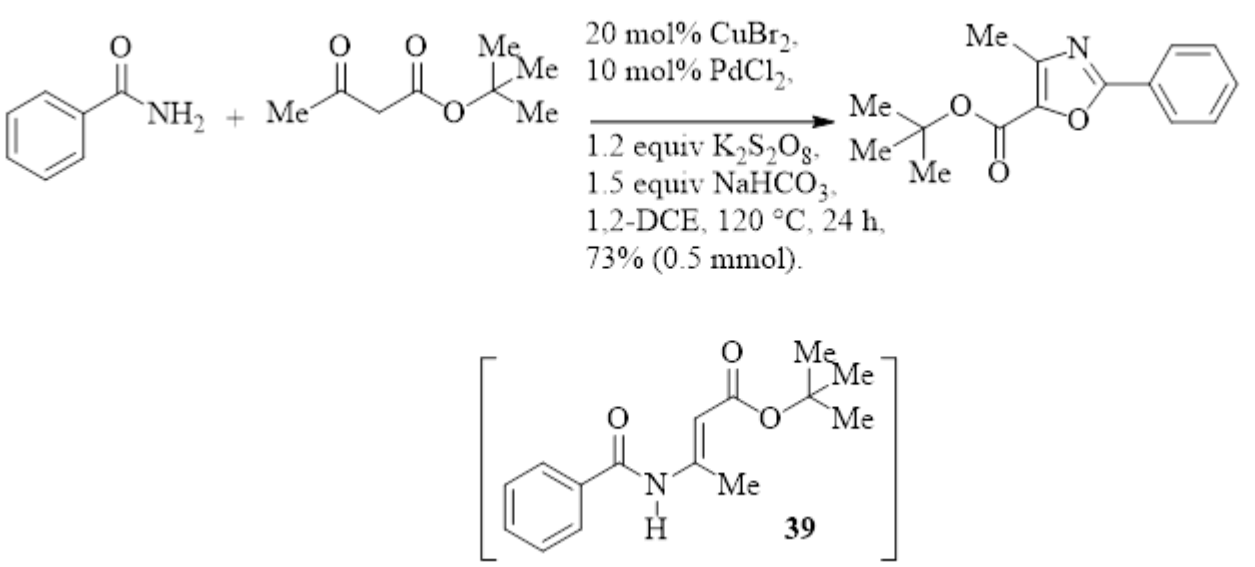
[25] R. Martin, A. Cuenca, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 5521-5524.

[26] C. W. Cheung, S. L. Buchwald, *J. Org. Chem*. **2012**, *77*, 7526-7537.



SCHEME 15

More recently, a Pd(II)-catalyzed C-H activation/C-O cyclization procedure has been published to prepare trisubstituted oxazoles in efficient manner from amides and ketones, as reported in Scheme 16.[27] From amides and ketones, it was postulated that Pd(II)-catalyst in the presence of $K_2S_2O_8$ promoted a dehydration condensation to furnish the corresponding enamide intermediates, such as **39**.



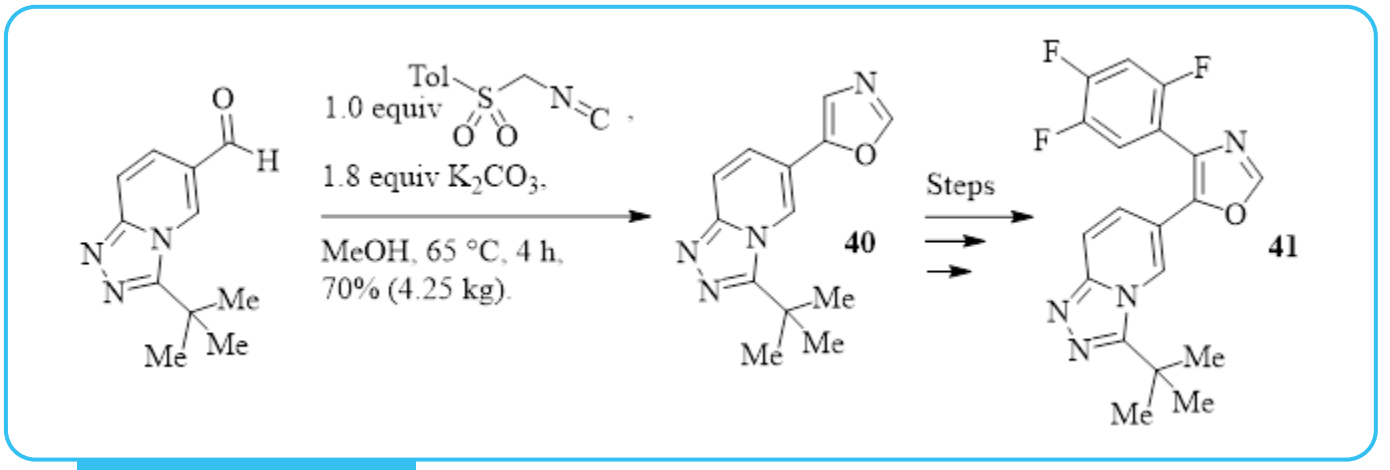
SCHEME 16

[27] M. Zheng, L. Huang, H. Huang, X. Li, W. Wu, H. Jiang, *Org. Lett.* **2014**, *16*, 5906-5909.

Van Leusen's reagent

para-Tosylmethyl isocyanide (TosMIC, see Scheme 17), a unique powerful synthon is also known as Van Leusen's reagent. This synthon presents three functionalized groups including the isocyanide and sulfonyl groups and a α-CH_2 easily deprotonated.[28] Since 1972, this commercially available stable odorless solid (~100 €/100 gr) has been largely used to prepare a diverse range of heterocycles, in particular oxazoles as presented in the following Schemes.

During the development of the 4,5-disubstituted oxazole **41**, a potent and selective inhibitor of the stress-activated kinase p38α, a robust, efficient and scalable synthesis of the oxazole scaffold **40** was optimized as described in Scheme 17.[29]



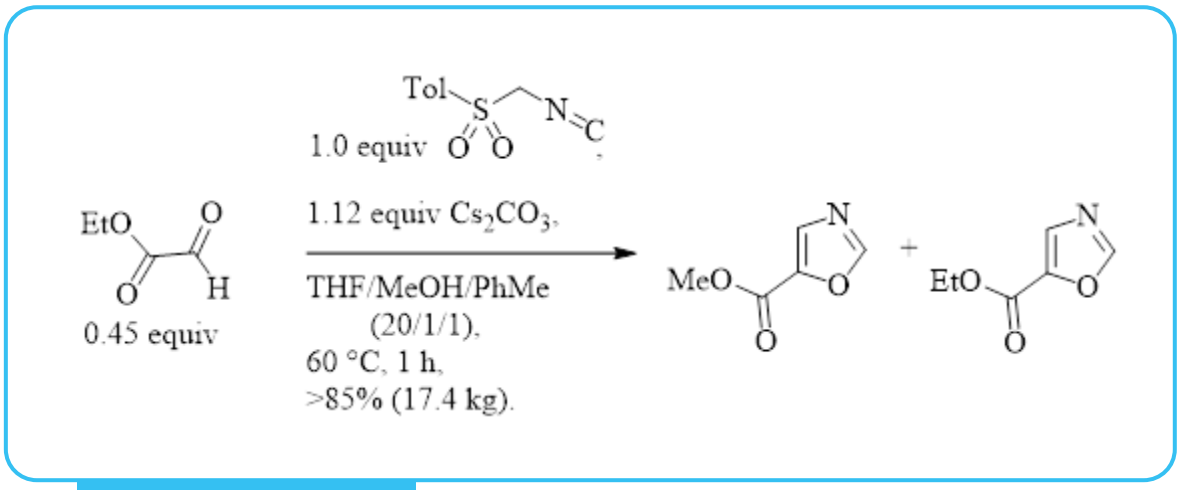
SCHEME 17

Another multikilogram scale synthesis of oxazole derivatives is presented in Scheme 18, from TosMIC and ethyl glyoxylate.[30] Methanol compared to ethanol provided faster conversion and was used as a solvent, even if partial transesterification occurred. It should be noted that the ester function was reduced at later stage into the corresponding primary alcohol.

[28] X. Zheng, W. Liu, D. Zhang, *Molecules* **2020**, *25*, 1594.

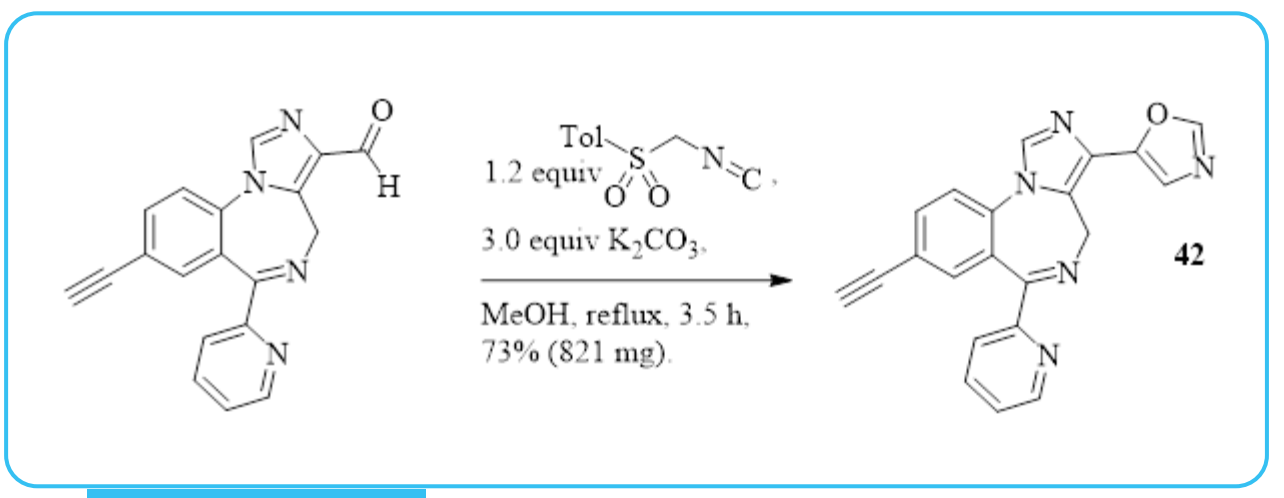
[29] B. Li, R. A. Buzon, Z. Zhang, *Org. Process Res. Dev*. **2007**, *11*, 951-955.

[30] D. Edney, D. G. Hulcoop, J. H. Leahy, L. E. Vernon, M. D. Wipperman, R. N. Bream, M. R. Webb, *Org. Process Res. Dev.* **2018**, *22*, 368-376.



SCHEME 18

The promising lead compound **42** for the treatment of anxiety disorders, has been prepared with the van Leusen's reagent, as mentioned in Scheme 19.[31]



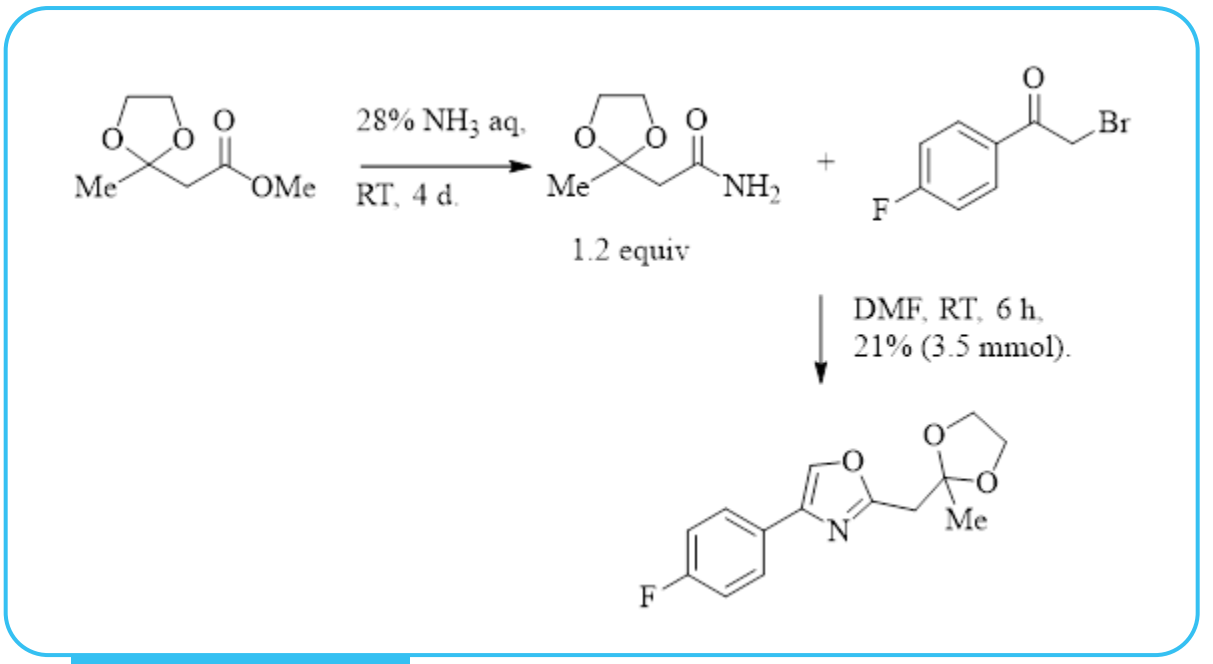
SCHEME 19

Blümlein-Lewy condensation

The Blümlein-Lewy oxazoles synthesis involves the condensation of amides with α-halo or α-hydroxy ketones.

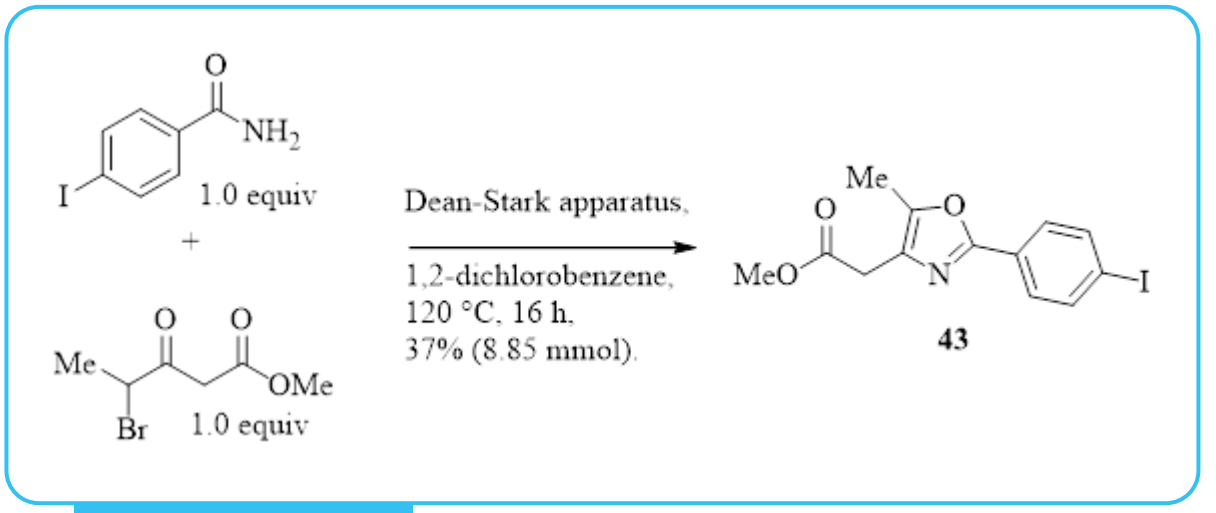
As part of the search for new highly potent herbicide safeners, a series of novel substituted phenyl oxazole derivatives has been prepared based on the Blümlein-Lewy condensation, as presented in Scheme 20.[32]

[31] J. M. Schkeryantz *et al*., *J. Med. Chem.* **2016**, *59*, 10800-10806.
[32] Y. Fu, D. Zhang, T. Kang, Y.-Y. Guo, W.-G. Chen, S. Gao, F. Ye, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 570-576.



SCHEME 20

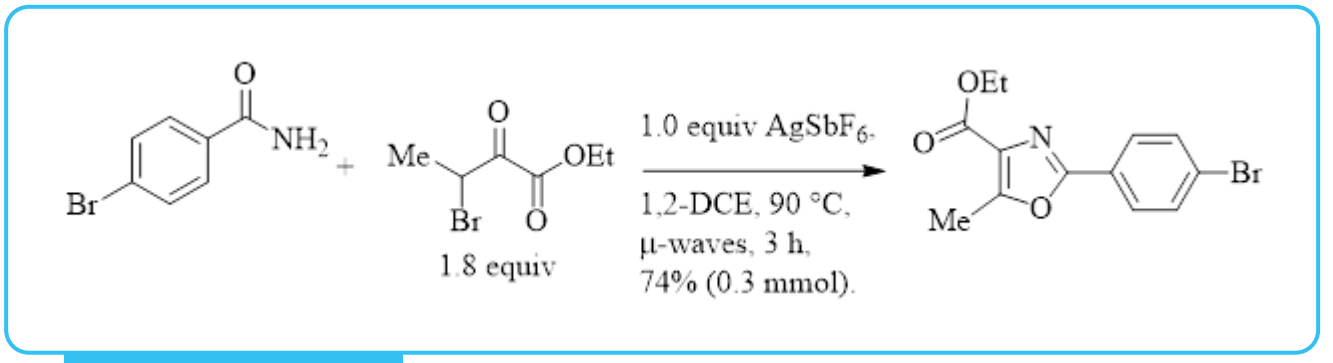
As highlighted in Scheme 21, the oxazole core of a PPARγ ligand **43** for radionuclide imaging *in vivo* studies was prepared using a Blümlein-Lewy condensation.[33]



SCHEME 21

[33] B. C. Lee, K. C. Lee, H. Lee, R. H. Mach, J. A. Katzenellenbogen, *Bioconjugate Chem*. **2007**, *18*, 514-523.

As presented in this paragraph, Blümlein-Lewy condensation is an attractive procedure to prepare oxazoles due to the ready availability of both partners and straightforward experimental conditions. Nevertheless, reported reactions show low yields, also Moses improved significantly the efficiency of this transformation in the terms of reaction yield by the addition of silver salts, as outlined in Scheme 22.[34] It was postulated that the halophilicity of the silver salt activates the α-bromo-group favoring the nucleophilic attack by the amide.



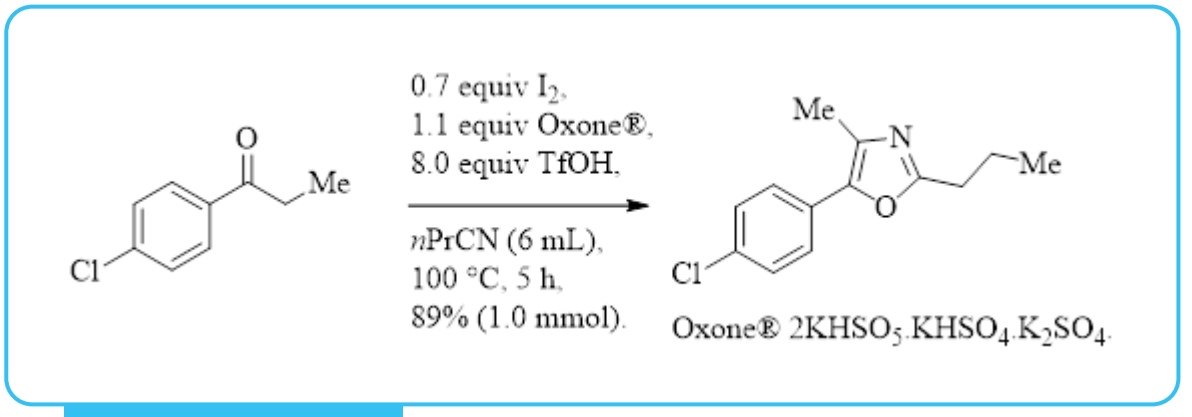
SCHEME 22

Iodine-mediated preparation of substituted oxazoles

Molecular iodine as well as iodine derivatives associated with different oxidative state are very efficient reagents to construct oxazole scaffolds.[35] Some examples of transition-metal-free green and sustainable preparation of oxazoles are presented in this paragraph.

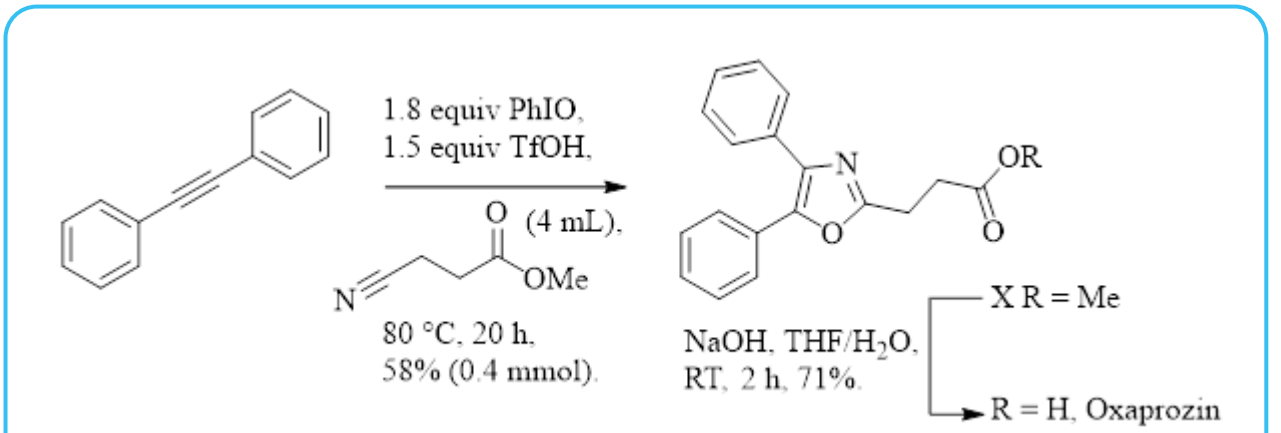
Togo *and Coll*. developed an iodine-mediated synthesis of 2,5-disubstituted and 2,4,5-trisubstituted oxazoles from aromatic ketones in the presence of oxone® and trifluoromethanesulfonic acid (TfOH) with nitriles, such as acetonitrile, propionitrile, butyronitrile, isobutyronitrile, and benzonitrile, used as solvent (Scheme 23).[36] In this transformation, α-iodoketones generated by *in situ* iodination, were oxidized into the corresponding α-iodosylketones which by reaction with the nitrile solvents provided the nitrilium intermediates leading then to rapid intramolecular cyclization.

[34] D. J. Ritson, C. Spiteri, J. E. Moses, *J. Org. Chem.* **2011**, *76*, 3519-3522.
[35] For an excellent review on this field, see: S. Dhawan, V. Kumar, P. S. Girase, S. Mokoena, R. Karpoormath, *ChemistrySelect* **2021**, *6*, 754-787.
[36] S. Imai, H. Kikui, K. Moriyama, H. Togo, *Tetrahedron* **2015**, *71*, 5267-5274.



SCHEME 23

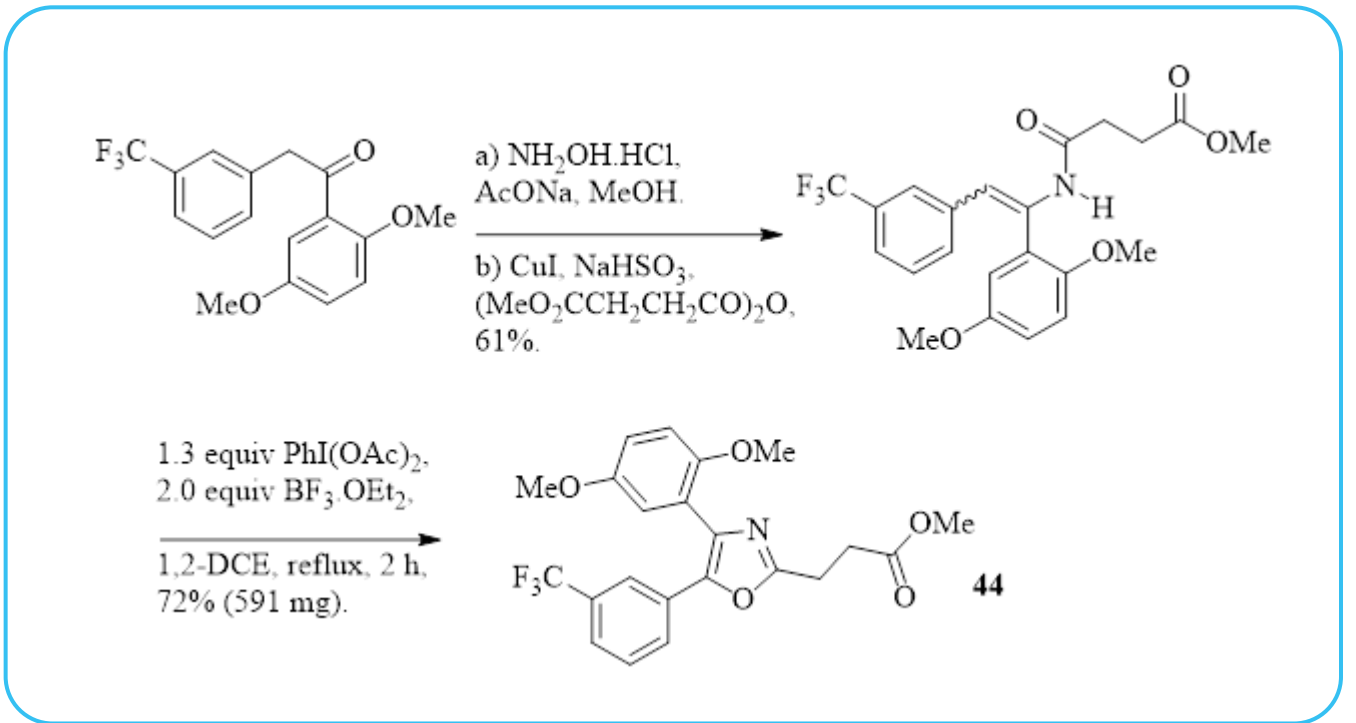
Starting with both terminal and internal alkynes and nitriles, an iodine(III)-mediated [2+2+1] cycloaddition through *in situ* formation of PhI(OH)OTf from iodosobenzene and triflic acid, a regioselective preparation of 2,4-disubstituted and 2,4,5-trisubstituted oxazoles has been reported.[37] This efficient methodology is illustrated through the synthesis of Oxaprozin, as outlined in Scheme 24. Further, it is interesting to note that the proposed mechanism would involve the formation of an alkenyliodonium triflate key intermediate which was isolated and characterized by single-crystal X-ray structure analysis. It is worth mentioning that the weakness of these two previous methodologies is the use of the nitrile partners as solvent.



SCHEME 24

[37] A. Saito, Y. Taniguchi, Y. Kambara, Hanzawa, *Org. Lett.* **2013**, *15*, 2672-2675.

A phenyliodine diacetate-mediated intramolecular oxidative cyclization of 2,4,5-trisubstituted oxazoles from various enamides through intramolecular oxidative annulation in the presence of boron trifluoride etherate has been developed (see Scheme 25 with the preparation of the Oxaprozin analogue **44**).[38] These reaction conditions were applied to a broad range of substituted enamides (readily accessible from known chemistry) yielded corresponding oxazoles in modest to good yields (40-90%).

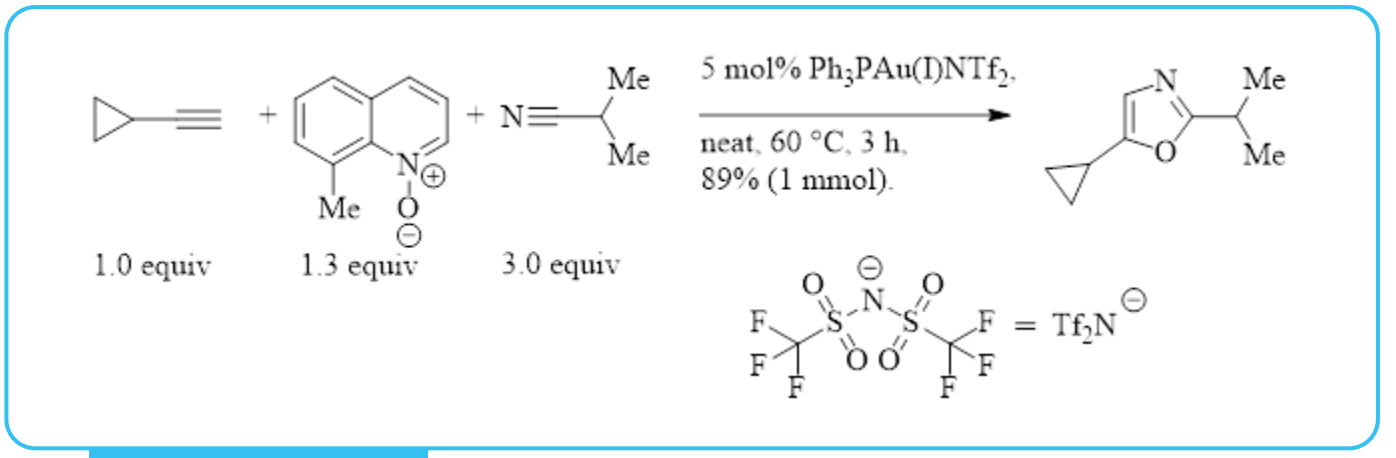


SCHEME 25

Gold-mediated preparation of oxazoles

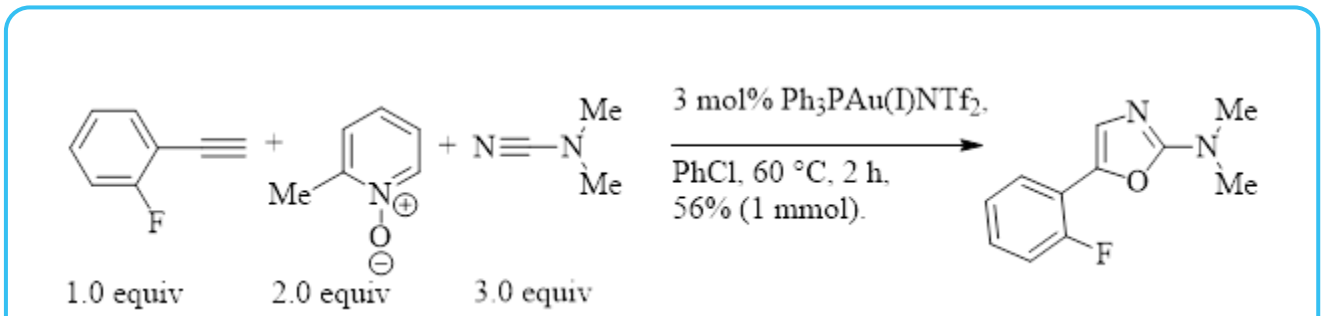
In this field, an elegant preparation of 2,5-disubstituted oxazoles involving a gold(I)-catalyzed [2+2+1] annulation of terminal alkynes, nitriles, and quinoline *N*-oxides as the oxygen atom source has been published by Zhang *and Coll*. as presented in Scheme 26.[39]

[38] Y. Zheng, X. Li, C. Ren, Daisy Z.-N., Y. Du, K. Zhao, *J. Org. Chem*. **2012**, *77*, 10353-10361.
[39] W. He, C. Li, L. Zhang, *J. Am. Chem. Soc*. **2011**, *133*, 8482-8485.



SCHEME 26

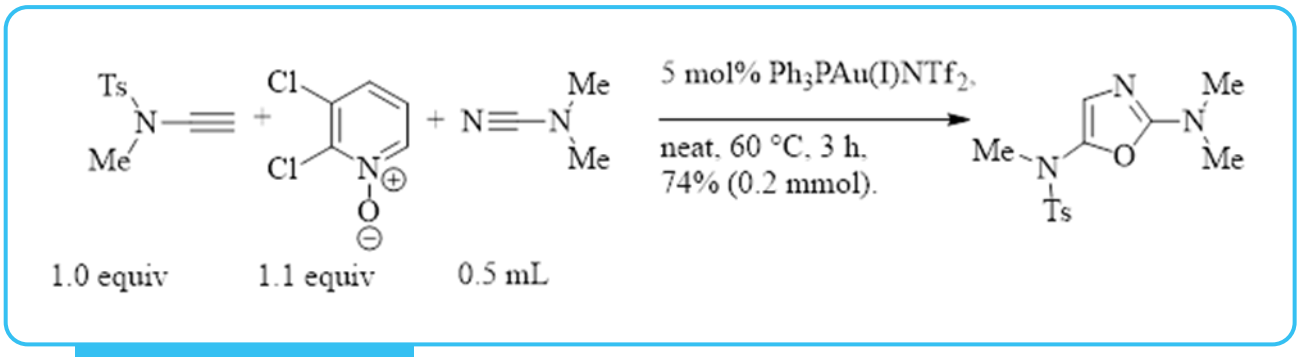
Later on, this gold-catalyzed heterocyclization of terminal alkynes was extended to cyanamides as outlined in Scheme 27, providing substituted 2-amino-5-oxazole derivatives.[40]



SCHEME 27

Very recently, the same authors applied the previous protocols with ynamide partners, instead of terminal alkynes, to efficiently prepare 2,5-diaminooxazoles, as exposed in Scheme 28. [41]

[40] V. A. Rassadin, V. P. Boyarskiy, V. Y. Kukushkin, *Org. Lett.* **2015**, *17*, 3502-3505.
[41] D. P. Zimin, D. V. Dar'in, V. Yu. Kukushkin, A. Y. Dubovtsev, *J. Org. Chem.* **2021**, *86*, 1748-1757.

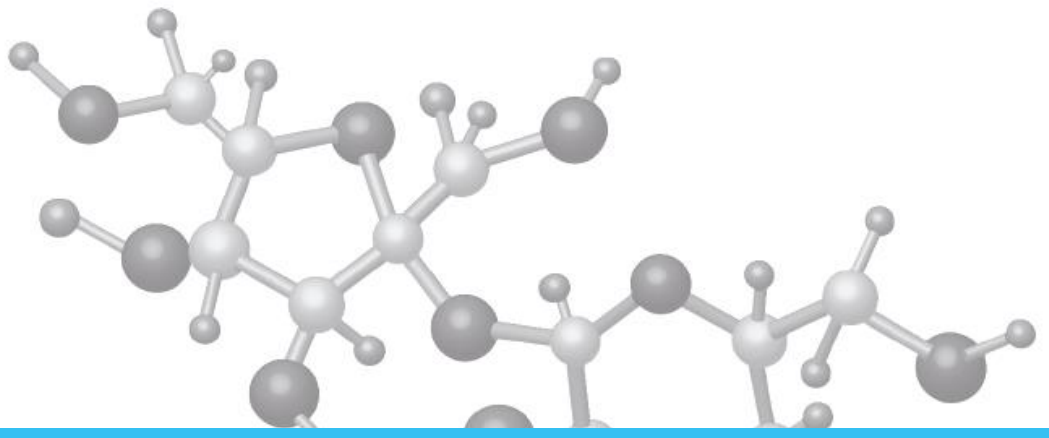


SCHEME 28

Conclusion

There is always room to improve current methodologies to efficiently prepare highly functionalized oxazoles, and new protocols involving flow chemistry and metal-free catalysis could emerged as interesting alternative with more advantages, such as selectivity and substrate tolerance.

I would like to thank Benoit Sicard for fruitful discussions and comments. I also warmly thank my colleagues, Dr. Sylvie Archambaud, Dr. Aude Vibert, Dr. Thibaut Martinez, Dr. Thomas Glachet and Dr. Julien Farard from AtlanChim Pharma for their valuable suggestions during the preparation of this manuscript. A special thanks to Lionel Bidet for linguistic assistance.



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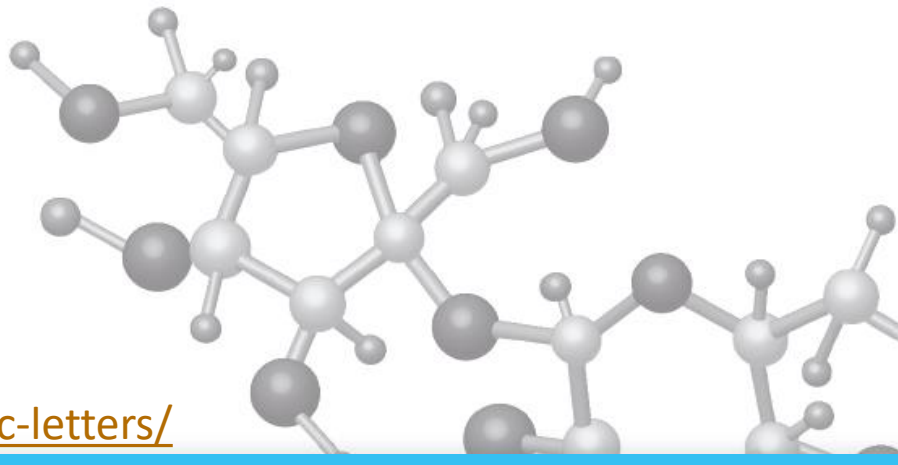

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