OL Organic Letters

pubs.acs.org/OrgLett Letter

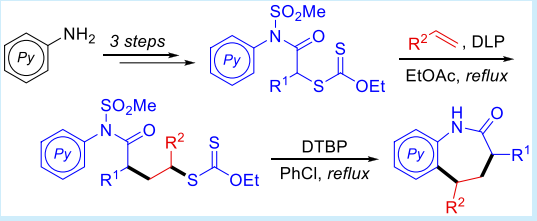
Modular Approach to Substituted Pyridoazepinones

Valentin S. Dorokhov and Samir Z. Zard*

Cite This: *Org. Lett.* 2021, 23, 2164–2168 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Pyridoazepinones are potentially interesting structures, yet they are still underexploited in the medicinal chemistry field and hard to obtain synthetically. We present a general and flexible synthetic route to substituted pyridoazepinones, enabled by the xanthate addition−transfer process, which furnishes the target molecules from readily available starting materials in generally good yields. The method shows good functional group tolerance and allows the preparation of pyridoazepinone scaffolds on gram scale.



The pyridine ring is one of the most common subunits in pharmaceuticals and agrochemicals. It also appears in a variety of fused scaffolds possessing a myriad of medicinal properties. Thus, the search for efficient and reliable strategies toward pyridine-containing structures represents an important challenge in organic chemistry.

Pyridoazepinones constitute such scaffolds. They are present in nature as fragments of biologically active substances, for example in adina alkaloids, isolated from *Adina rubescens* (Figure 1).[1] Synthetic derivatives of this class

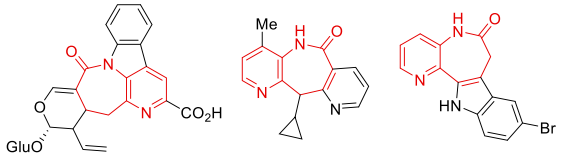


Figure 1. Some biologically active pyridoazepinones

include Nevirapine, a non-nucleoside inhibitor of HIV reverse transcriptase.[2] Nevirapine was approved in 1996 by the FDA and is currently in the WHO List of Essential Medicines. Another medicinally active pyridoazepinone is 1-azakenpaullone, which inhibits glycogen synthase kinase 3, a therapeutic target in the development of antidiabetic drugs.[3]

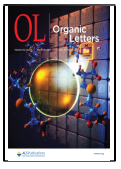
Finally, pyridoazepinones are classical isosteres of benzazepinones, which are an important family of biologically active compounds (they act, for example, as sodium channel blockers).[4] Thus, it would be desirable to make nitrogen-containing analogues of various biologically active benzazepinones. This sort of modification may result in better binding with protein active sites and in improved pharmacokinetic properties.

This being said, however, it was surprising to find that no general method for the synthesis of these structures has been established, even though the first record of obtaining such compounds dates from 1969.[5] The most common method to access pyridoazepinones is based on ring expansion reactions, such as the Beckmann and Schmidt rearrangements (Scheme 1A).[6]

However, in most cases, this strategy requires the preparation of highly functionalized substrates and incudes *de novo* pyridine ring formation. Furthermore, the variety of structures that can be attained by this route is limited due to low functional group tolerance. The same problems arise when the seven-membered ring is constructed via a Dieckmann condensation (Scheme 1A).[3,7] Even though these methods have furnished target materials for biological evaluations, they lack flexibility and do not allow the preparation of the large libraries of compounds needed for drug discovery. A completely different method, based on palladium-catalyzed C−H arylation, was described by Cramer and co-workers.[8] Being tailored mostly for the preparation of benzazepinones containing quaternary stereocenters in the seven-membered ring, this method also allowed the synthesis of pyridoazepinone. However, only one example was reported and the reaction required harsh conditions and a high catalyst loading. Summing up the above, a new, practical, and convergent approach to pyridoazepinones would be highly valuable.

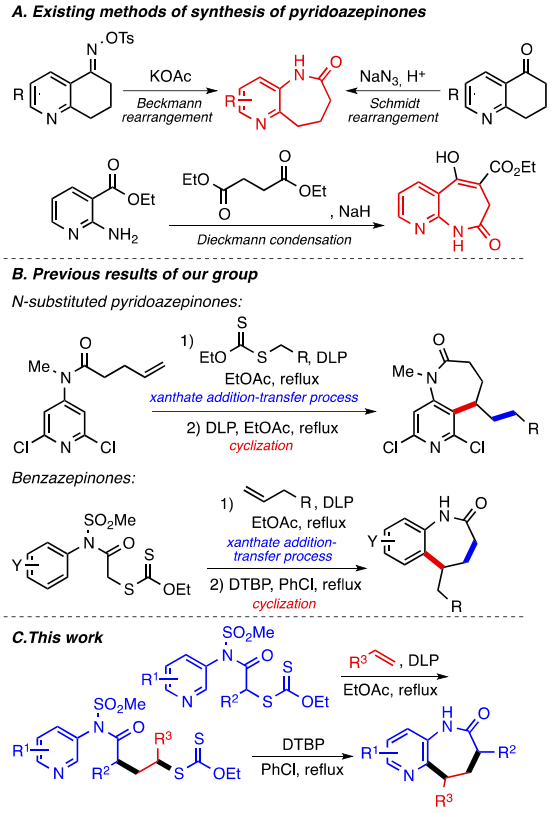
Following a longstanding interest in the synthesis of heterocyclic scaffolds in our group,[9] we developed a few pathways to benzazepinones[10] and *N*-alkyl-substituted pyridoazepinones[11] (Scheme 1B). In this paper, we present a general and modular synthesis of *N-unsubstituted* pyridoazepinones. Our method features the construction of the seven-

Received: January 27, 2021
Published: March 2, 2021



https://dx.doi.org/10.1021/acs.orglett.1c00321
Org. Lett. 2021, 23, 2164–2168

Scheme 1. Methods for the Synthesis of Pyridoazepinones

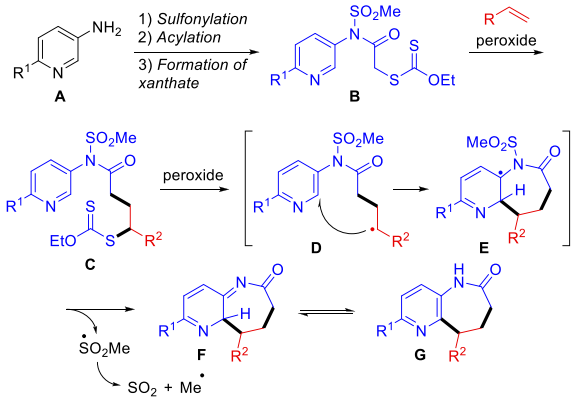


membered ring by C−C bond formation via a xanthate addition−transfer process, radical cyclization, and rearomatization of the pyridine ring enabled by homolytic cleavage of the sulfonamide bond (Scheme 1C).

The synthesis of pyridoazepinones from simple precursors must address several challenges. First, the formation of seven-membered rings is a rather unfavorable process, due to low reaction rates[12] that may result in lower yields and the formation of side products. Additionally, the pyridine moiety is more electron-deficient but is less aromatic than the benzene ring, making the final oxidative aromatization step more difficult. Finally, the most interesting examples of this family possess a secondary amide group, which can partake in constructive hydrogen bonding within the receptor or be used as an additional functionalization site. However, an *N*-monosubstituted amide can also be a drawback because it adopts an E conformation that prevents the cyclization, as shown by our previous reports;[10] thus, a protecting group is required that can be easily removed, preferably during the last step of synthesis.

According to our method, substituted aminopyridines **A** can be converted into xanthates **B** by a simple sequence that includes sulfonylation, introduction of α-chloroacetyl group, and xanthate formation (Scheme 2). Due to the high commercial availability of substituted aminopyridines and the ease of preparation of xanthates, a vast array of starting materials can be synthesized in principle. The next step is the peroxide-promoted intermolecular radical addition of xanthate **C** to an unactivated olefin, which can bear various functional groups. The xanthate addition−transfer process leads to another, more complex xanthate **C**, which in turn gives a radical **D** when treated with peroxide at high temperature. The following intramolecular addition results in the

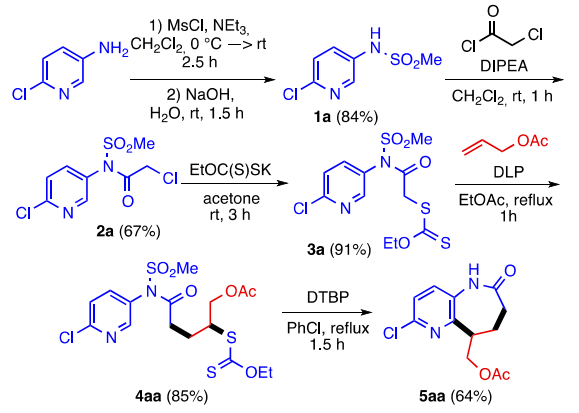
Scheme 2. Proposed Strategy toward Pyridoazepinones



formation of delocalized dihydropyridinyl radical **E**, in which the fragmentation of the N−S bond occurs to give intermediate **F** with extrusion of a methanesulfonyl radical. This latter species can extrude sulfur dioxide to furnish a methyl radical that can participate in the chain propagation. As for intermediate **F**, it rapidly undergoes a tautomerization to yield the desired pyridoazepinone **G**. This last fragmentation thus serves to rearomatize the pyridine ring and furnish at the same time the *N-unsubstituted* seven-membered ring lactam.

For the starting point for our studies, we chose 2-chloro-5-aminopyridine because our previous experience showed the utility of a substituent on position 2 in curtailing the nucleophilicity of the pyridine nitrogen and preventing an ionic destruction of the xanthate group.[10] Following this consideration, we converted 2-chloro-5-aminopyridine into the corresponding xanthate **3a** via a simple three-step sequence, with each step proceeding in good to excellent yield (Scheme 3). It is also worth noting that the reactions

Scheme 3. First Example of Pyridoazepinone Synthesis



were carried out on multigram scale. All the materials are crystalline and can be easily purified by recrystallization, which makes this procedure highly suitable for further scaling up.

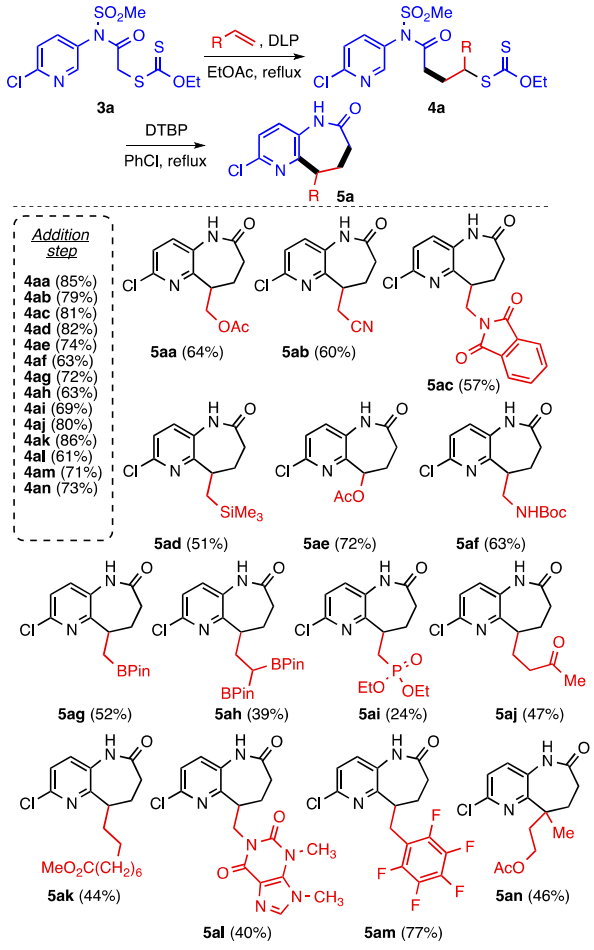
The resulting xanthate **3a** was then introduced into a test reaction with allyl acetate, under thermal conditions with substoichiometric amounts of dilauroyl peroxide (DLP) as the initiator (10 mol %; DLP is also sold under lauroyl peroxide, Laurox, or Luperox). This reaction proceeded with very good yield (85%), and the isolated adduct **4aa** was

https://dx.doi.org/10.1021/acs.orglett.1c00321
Org. Lett. 2021, 23, 2164−2168

purified by column chromatography. We next examined the ability of this xanthate to undergo the desired key cyclization reaction. Based on our previous experience, a higher temperature is usually required to induce the cleavage of the sulfonamide moiety, and DLP was therefore replaced with the more thermally robust di-*tert*-butyl peroxide (DTBP). After screening three high-boiling solvents (chlorobenzene, *tert*-butylbenzene, and octane), we found that the best results were obtained with chlorobenzene. To our delight, the target pyridoazepinone **5aa** was produced in good yield (64%).

We next expanded the study to other olefins (Scheme 4). Model xanthate **3a**, derived from 2-chloro-5-aminopyridine,

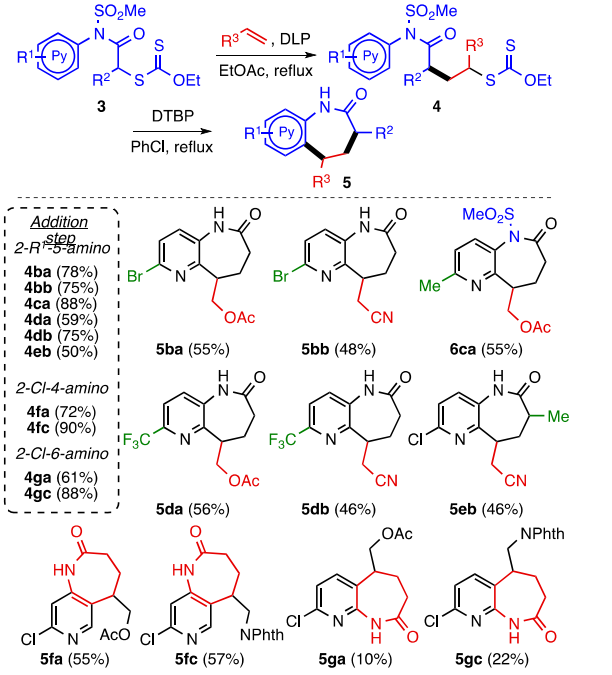
Scheme 4. Olefin Scope



reacted readily with various alkenes, and the cyclization provided pyridoazepinones bearing different substituents, including esters, protected amines, boronate esters, silanes, and more complex structures like purines. 1,1-Disubstituted alkenes can also be used, leading to the creation of a quaternary center, as indicated by example **5an**. The fact that the intermolecular addition step to electronically unbiased alkenes proceeds in higher yield than the cyclization step underscores the general difficulty of producing a seven-membered ring by direct radical ring closure, and even more so when the cyclization is onto an aromatic or heteroaromatic nucleus. It is also worth noting that, in the absence of alkene, treatment of xanthates such as **B** (Scheme 2) leads to azaoxindoles,[11] but even this ring-closure mode appears to be slower than the intermolecular addition to the alkene and does not therefore cause any significant complications in the present context.

We also explored the scope of the pyridines that can be involved in this sequence (Scheme 5). Thus, we prepared

Scheme 5. Scope of Pyridines



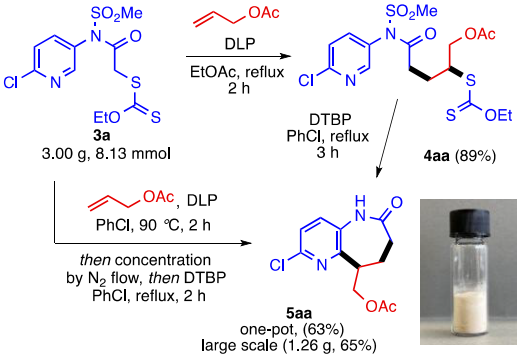
four xanthates, bearing bromo (**3b**), methyl (**3c**), and trifluoromethyl substituents (**3d**) in the 2-position of the pyridine ring and, finally, a methyl group in the α-position to the carbonyl group (**3e**) (see Supporting Information for details). In the case of xanthates **3b**, **3d**, and **3e** we were glad to find that both the radical addition and cyclization steps proceeded with moderate to good yields; for xanthate **3c**, however, we quite surprisingly isolated only the sulfonylated product **6ca**. In this case, the oxidation of the intermediate radical (radical **E** in Scheme 2) seems to be more favorable than the extrusion of methanesulfonyl radical, for as yet unknown reasons.

The regioisomeric products **5fa**, **5fc**, **5ga**, and **5gc**, derived from 4-amino-2-chloropyridine and 6-amino-2-chloropyridine, were also prepared in the same manner. Even though xanthates **4fa** and **4fc** readily cyclized to the 3-position of the pyridine ring, the reaction proved to be more problematic in the case of the products **5ga** and **5gc**, giving a mixture of unidentifiable side products. In order to improve the yield, we tried to perform the cyclization of xanthate **4gc** under microwave heating. However, no increase of the yield was found. We also conducted the reaction in the presence of camphorsulfonic acid (CSA), bearing in mind the assumption that the protonated pyridine nucleus should react faster ("Minisci-type" reaction conditions). Unfortunately, no improvement in the yield was observed either, and the reaction merely resulted in hydrolysis of the amide bond of most of the starting xanthate **4gc**. The reasons for the delinquent behavior of the 2-chloro-6-amino- series are not clear at the moment, and further work is needed to probe this question.

https://dx.doi.org/10.1021/acs.orglett.1c00321
Org. Lett. 2021, 23, 2164−2168

To highlight further the practicality of our approach, we performed the sequence leading to benzazepinone **5aa** in a one-pot process, which furnished the desired product in a somewhat better overall yield (Scheme 6). We also prepared

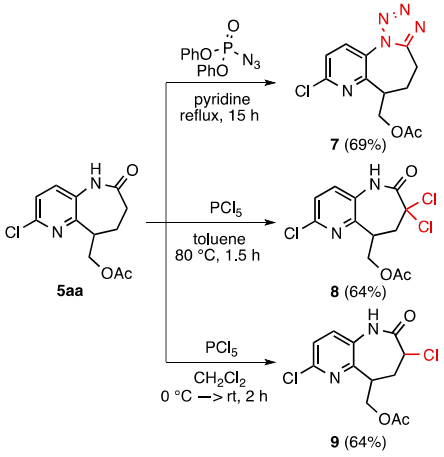
Scheme 6. One-Pot and Gram-Scale Synthesis



pyridoazepinone **5aa** from xanthate **3a** on gram scale, affording 1.26 g of the target product (Scheme 6). In this case, the purification of the product consisted of a single precipitation from the concentrated reaction mixture instead of column chromatography.

Finally, to demonstrate the utility of the pyridoazepinone scaffold for medicinal chemistry, we tried to prepare several derivatives of compound **5aa**, exploiting the presence of the secondary amide function (Scheme 7). Tetrazoles belong to

Scheme 7. Derivatization of Pyridoazepinones



an interesting class of pharmacophore groups and are present in various medicaments.[13] Thus, we prepared tetrazole **7** using the method reported recently by Matsugi and co-workers.[14] Another possible modification of pyridoazepinones relies on the functionalization of the α-position of the amide via the corresponding Vilsmeier salt. Thus, treatment with phosphorus pentachloride furnished dichlorolactam **8** in good yield. Interestingly, under milder conditions, the monochlorinated product **9** is fortuitously produced in the same yield.

In conclusion, we have developed a modular and scalable synthesis of pyridoazepinones, exploiting cheap and readily available starting materials and reagents. Most of the structures described in the preceding schemes would be quite difficult to obtain by more traditional routes. Indeed, it is the relative inaccessibility of pyridoazepinones that has hitherto hampered their more extensive exploitation by medicinal chemists. It is hoped that the present work will contribute to eliminating this barrier and encourage the incorporation of such structures in the design of biologically active substances.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00321.

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Samir Z. Zard − *Laboratoire de Synthèse Organique, CNRS, UMR 7652, Ecole Polytechnique, Palaiseau, Cedex 91128, France;* orcid.org/0000-0002-5456-910X; Email: samir.zard@polytechnique.edu

Author

Valentin S. Dorokhov − *Laboratoire de Synthèse Organique, CNRS, UMR 7652, Ecole Polytechnique, Palaiseau, Cedex 91128, France*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00321

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is affectionately dedicated to Professor Ilhyong Ryu on the occasion of his 70th birthday. We also respectfully dedicate it to the memory of our friends: Professors Robert M. Williams (Colorado State University), François Diederich (ETH, Switzerland), Chris Abell (University of Cambridge), François Mathey (NTU, Singapore and Zhengzhou University, China), and Victor Snieckus (Queens University, Kingston, Canada). We gratefully acknowledge financial support by the ANR (project SULFA) and thank Dr Sophie Bourcier (Laboratoire de Chimie Moléculaire, Ecole Polytechnique) for recording the high-resolution mass spectra.

■ REFERENCES

(1) Brown, R. T.; Fraser, S. B. Adina Alkaloids: Desoxycordifoline Lactam. *Tetrahedron Lett.* **1973**, *14* (11), 841−842.

(2) (a) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridobenzo- and Dipyridodiazepinones. *J. Med. Chem.* **1991**, *34* (7), 2231−2241. (b) De Corte, B. L. From 4,5,6,7-Tetrahydro-5-Methylimidazo-[4,5,1-Jk](1,4) Benzodiazepin-2(1H)-One (TIBO) to Etravirine (TMC125): Fifteen Years of Research on Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. *J. Med. Chem.* **2005**, *48* (6), 1689−1696.

(3) (a) Kunick, C.; Lauenroth, K.; Leost, M.; Meijer, L.; Lemcke, T. 1-Azakenpaullone Is a Selective Inhibitor of Glycogen Synthase Kinase-3β. *Bioorg. Med. Chem. Lett.* **2004**, *14* (2), 413−416. (b) Stukenbrock, H.; Mussmann, R.; Geese, M.; Ferandin, Y.; Lozach, O.; Lemcke, T.; Kegel, S.; Lomow, A.; Burk, U.; Dohrmann, C.; Meijer, L.; Austen, M.; Kunick, C. 9-Cyano-1-Azapaullone (Cazpaullone), a Glycogen Synthase Kinase-3 (GSK-3) Inhibitor Activating Pancreatic β Cell Protection and Replication. *J. Med. Chem.* **2008**, *51* (7), 2196−2207. (c) Egert-Schmidt, A.-M.; Dreher, J.; Dunkel, U.; Kohfeld, S.; Preu, L.; Weber, H.; Ehlert, J. E.; Mutschler, B.; Totzke, F.; Schächtele, C.; Kubbutat, M. H. G.; Baumann, K.; Kunick, C. Identification of 2-Anilino-9-Methoxy-5,7-Dihydro-6 H -Pyrimido[5,4-d][1]Benzazepin-6-Ones as Dual PLK1/VEGF-R2 Kinase Inhibitor Chemotypes by Structure-Based Lead Generation. *J. Med. Chem.* **2010**, *53* (6), 2433−2442.

(4) Hoyt, S. B.; London, C.; Abbadie, C.; Felix, J. P.; Garcia, M. L.; Jochnowitz, N.; Karanam, B. V.; Li, X.; Lyons, K. A.; McGowan, E.; Priest, B. T.; Smith, M. M.; Warren, V. A.; Thomas-Fowlkes, B. S.; Kaczorowski, G. J.; Duffy, J. L. A Novel Benzazepinone Sodium Channel Blocker with Oral Efficacy in a Rat Model of Neuropathic Pain. *Bioorg. Med. Chem. Lett.* **2013**, *23* (12), 3640−3645.

(5) Herbert, R.; Wibberley, D. G. Syntheses and Properties of 1H-Pyrrolo[2,3-b]Pyridines. *J. Chem. Soc. C* **1969**, No. 11, 1505−1514.

(6) (a) Jössang-Yanagida, A.; Gansser, C. Tetrahydropyridoazepines and Tetrahydropyridoazepinones from the Corresponding Dihydroquinolones. *J. Heterocycl. Chem.* **1978**, *15* (2), 249−251. (b) Maquestiau, A.; van Haverbeke, Y.; Vanden, J.-J E.; De Pauw, N. Étude Du Comportement D'Oximes de 7,8-Dihydroquinoléine-5 (6H) - Ones Lors de La Réaction de Beckmann. *Bull. Soc. Chim. Belg.* **1980**, *89* (1), 45−50. (c) Gatta, F.; Pomponi, M.; Marta, M. Synthesis of 7,8-dihydro-6H-pyrazolo[3,4-b]Quinolin-5-ones and Related Derivatives. *J. Heterocycl. Chem.* **1991**, *28* (5), 1301−1307. (d) Tolkunov, S. V.; Khyzhan, A. I.; Dulenko, V. I. Anomalous Beckmann Reaction of 4-Aryl-2,7,7-Trimethyl-5-Oxo-5,6,7,8- Tetrahydroquinoline Oximes in Polyphosphoric Acid. 1. New Synthesis of 1-Ethoxycarbonyl-2,5,5-Trimethyl-5,6-Dihydro-4H-Pyrido[2,3,4-k, l]-Acridines. *Chem. Heterocycl. Compd.* **2003**, *39* (12), 1627−1632. (e) Song, Y. H.; Joe, B. S.; Lee, H. M. Synthesis of 6,7,8,9-Tetrahydro-5*H*-1-Thia-5,10-Diaza-Cyclohepta[f]Inden-4-Ylamine Derivatives. *Heterocycl. Commun.* **2009**, *15* (3), 203−207. (f) Muylaert, K.; Jatczak, M.; Wuyts, B.; De Coen, L.; Van Hecke, K.; Loones, H.; Keemink, J.; García, D.; Mangelinckx, S.; Annaert, P.; Stevens, C. Synthesis and Early ADME Evaluation of a Novel Scaffold, Tetrahydro-6H-Pyrido[3,2-b]Azepin-6-One. *Synlett* **2014**, *25* (10), 1443−1447.

(7) Maiwald, F.; Benítez, D.; Charquero, D.; Dar, M. A.; Erdmann, H.; Preu, L.; Koch, O.; Hölscher, C.; Loaëc, N.; Meijer, L.; Comini, M. A.; Kunick, C. 9- and 11-Substituted 4-Azapaullones Are Potent and Selective Inhibitors of African Trypanosoma. *Eur. J. Med. Chem.* **2014**, *83* (2014), 274−283.

(8) Saget, T.; Cramer, N. Enantioselective C-H Arylation Strategy for Functionalized Dibenzazepinones with Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2013**, *52* (30), 7865−7868.

(9) (a) Zard, S. Z. The Xanthate Route to Pyridines. *Tetrahedron* **2020**, *76*, 130802. For recent reviews on the degenerative xanthate addition transfer process, see: (b) Quiclet-Sire, B.; Zard, S. Z. Fun with Radicals: Some New Perspectives for Organic Synthesis. *Pure Appl. Chem.* **2010**, *83*, 519−551. (c) Quiclet-Sire, B.; Zard, S. Z. On the Strategic Impact of the Degenerative Transfer of Xanthates on Synthetic Planning. *Isr. J. Chem.* **2017**, *57*, 202−217. (d) Zard, S. Z. Radical Alliances: Solutions and Opportunities for Organic Synthesis. *Helv. Chim. Acta* **2019**, *102*, No. e1900134.

(10) (a) Charrier, N.; Liu, Z.; Zard, S. Z. Desulfonylative Radical Ring Closure onto Aromatics. A Modular Route to Benzazepin-2-Ones and 5-Arylpiperidin-2-Ones. *Org. Lett.* **2012**, *14* (8), 2018−2021. (b) Quiclet-Sire, B.; Tran, N. D. M.; Zard, S. Z. An Unusual Synthesis of *N*-Unsubstituted Benzazepinones. *Org. Lett.* **2012**, *14*, 5514−5517.

(11) (a) Bacqué, E.; El Qacemi, M.; Zard, S. Z. Tin-Free Radical Cyclizations for the Synthesis of 7-Azaoxindoles, 7-Azaindolines, Tetrahydro[1,8]naphthyridines, and Tetrahydro-5H-pyrido[2,3-b]-azepin-8-Ones. *Org. Lett.* **2004**, *6* (21), 3671−3674. (b) Petit, L.; Botez, I.; Tizot, A.; Zard, S. Z. A Flexible Radical Approach to 5-Substituted 4,5-Dihydro-3H-Pyrido[4,3-b]Azepin-2-Ones. Some Mechanistic Observations on the Radical Cyclisation-Aromatisation Process. *Tetrahedron Lett.* **2012**, *53* (26), 3220−3224.

(12) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. Radical Cyclization Reactions. *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 1996; pp 301−856.

(13) Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. Medicinal Chemistry of Tetrazoles. *Russ. Chem. Bull.* **2012**, *61* (4), 768−780.

(14) Ishihara, K.; Shioiri, T.; Matsugi, M. An Expeditious Approach to Tetrazoles from Amides Utilizing Phosphorazidates. *Org. Lett.* **2020**, *22* (16), 6244−6247.

https://dx.doi.org/10.1021/acs.orglett.1c00321
Org. Lett. 2021, 23, 2164−2168