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An Unusual Synthesis of *N*-Unsubstituted Benzazepinones

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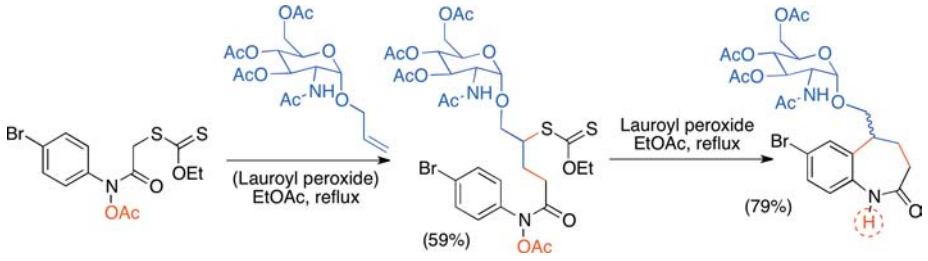
ABSTRACT



A short route to novel bicyclic *N*-unprotected benzazepinones is described starting from *N*-acetoxyanilides involving radical addition and cyclization with concomitant homolytic rupture of the N−O bond.

We describe here an unexpected route to *N*-unsubstituted benzazepinone we discovered while examining a radical-based approach to cyclic hydroxamic acids. The strong chelating ability of hydroxamic acids toward metal ions such as zinc has made them popular targets for medicinal chemists. Numerous members of this family have indeed been reported to be potent inhibitors of histone deacetylase and matrix metalloproteinases.[1] Other interesting biological properties include antibiotic, antifungal, anti-inflammatory and anticancer activities.[1,2] While most hydroxamic acids described are linear derivatives, such as the antibiotic fosmidomycin **1**, a few cases where the hydroxamate motif is part of a ring appear to be particularly interesting (Figure 1). Examples include cobactin T, a siderophore growth promoter isolated from mycobacteria,[3] and PF-04859989, **3**, an irreversible kynurenine aminotransferase II inhibitor developed by Pfizer for treating schizophrenia.[4]

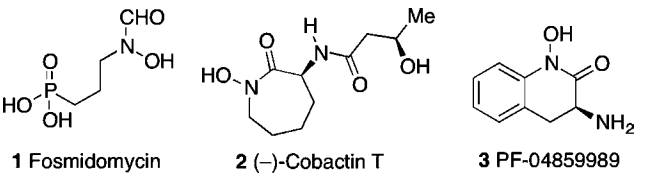


Figure 1. Examples of biologically active hydroxamic acids.

As part of our ongoing work on xanthates,[5] we found that lactams fused to aromatic or heteroaromatic rings could be readily constructed by direct radical cyclization

(1) (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. *Chem. Rev.* **1999**, *99*, 2735. (b) Rao, B. G. *Curr. Pharm. Des.* **2005**, *11*, 295. (c) Flipo, M.; Charton, J.; Hocine, A.; Dassonneville, S.; Deprez, B.; Deprez-Poulain, R. *J. Med. Chem.* **2009**, *52*, 6790.

(2) (a) Montgomery, J. I.; Brown, M. F.; Reilly, U.; Price, L. M.; Abramite, J. A.; Arcari, J.; Barham, R.; Che, Y.; Chen, J. M.; Chung, S. W.; Collantes, E. M.; Desbonnet, C.; Doroski, M.; Doty, J.; Engtrakul, J.; Harris, T. M.; Huband, M.; Knafels, J. D.; Leach, K. L.; Liu, S.; Marfat, A.; McAllister, L.; McElroy, E.; Menard, C. A.; Mitton-Fry, M.; Mullins, L.; Noe, N. C.; O'Donnell, J.; Oliver, R.; Penzien, J.; Plummer, M.; Shanmugasundaram, V.; Thoma, C.; Tomaras, A. P.; Uccello, D. P.; Vaz, A.; Wishka, D. J. *J. Med. Chem.* **2012**, *55*, 1662. (b) Tardibono, L. P., Jr.; Miller, M. J. *Org. Lett.* **2009**, *11*, 1575.

(3) Yang, S. −M.; Lag, B.; Wilson, L. J. *J. Org. Chem.* **2007**, *72*, 8123.

(4) Dounay, A. B.; Anderson, M.; Bechle, B. M.; Campbell, B. M.; Claffey, M. M.; Evdokimov, A.; Evrard, E.; Fonseca, K. R.; Gan, X.; Ghosh, S.; Hayward, M. M.; Horner, W.; Kim, J. −Y.; McAllister, L. A.; Pandit, J.; Paradis, V.; Parikh, V. D.; Reese, M. R.; Rong, S. B.; Salafia, M. A.; Schuyten, K.; Strick, C. A.; Tuttle, J. B.; Valentine, J.; Wang, H.; Zawadzke, L. E.; Verhoest, P. R. *ACS Med. Chem. Lett.* **2012**, *3*, 187.

(5) For reviews on the xanthate radical transfer reaction, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

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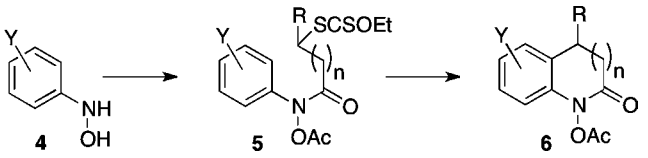
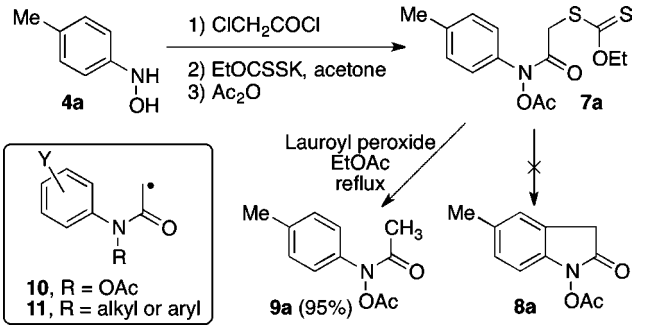
onto the aromatic nucleus.[6] It seemed therefore from the outset a simple matter to extend this approach to the synthesis of aryl-fused cyclic hydroxamic acids **6** as shown in Scheme 1. An appealing aspect of this route is the ready availability of the requisite precursors **5** from arylhydroxylamines **4**, which in turn can be easily prepared by partial reduction of nitroarenes.[7]

Scheme 1



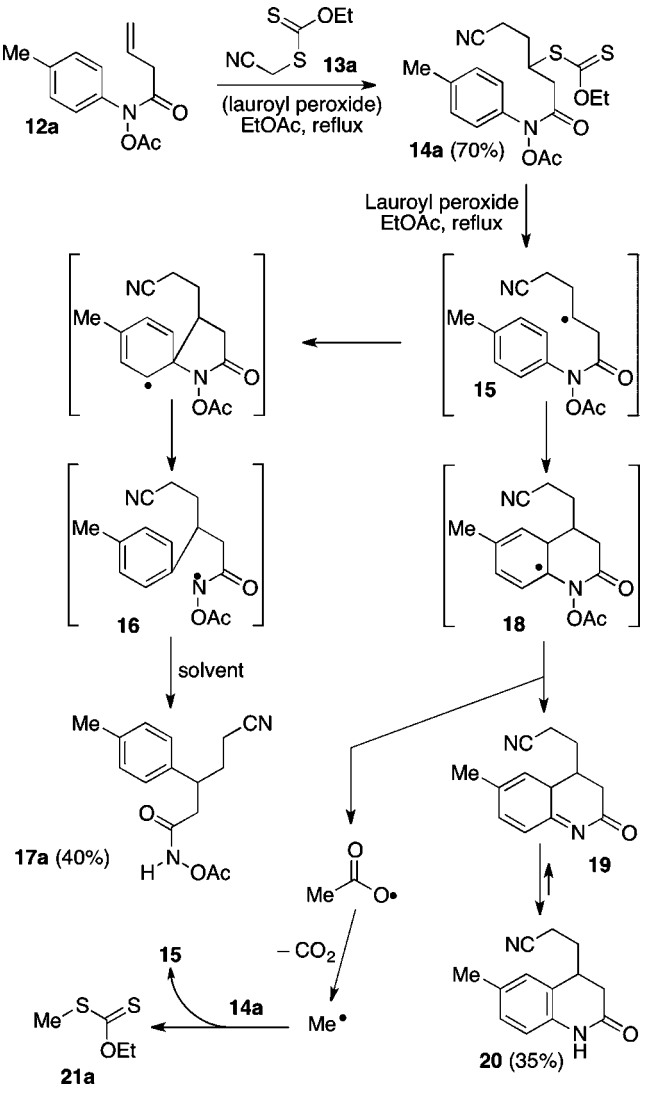
The formation of five-membered rings by radical cyclization is usually the most efficient, so we first attempted accessing *N*-hydroxyoxindoles (**6**, $n = 0$). The required xanthate precursor **7a** was prepared from *p*-methyl-phenylhydroxylamine **4a** by chloroacetylation of the nitrogen, displacement of the chlorine with potassium *O*-ethyl xanthate and acetylation (Scheme 2).

Scheme 2



Unfortunately, when a refluxing solution of this material in ethyl acetate was treated with lauroyl peroxide, added portion-wise in stoichiometric amounts, none of the desired *N*-acetoxy-oxindole **8a** was obtained; only the trivial reduced product **9a** was isolated in 95% yield.[8] For reasons that are not yet clear, but that may have to do with bond angles, the cyclization of radicals **10** onto the aromatic ring is apparently significantly slower as compared with the corresponding anilide radicals **11**, which ring-close efficiently under similar conditions.[6,9]

Scheme 3



In contrast, we found that the desired cyclization took place to a certain extent in the homologous series (**5**, **6**; $n = 1$) but not in the manner we had anticipated. Two major products were formed when compound **14a**, itself prepared by radical addition of cyanomethyl xanthate **13a** to butenyl hydroxamate **12a**, was subjected to the action of lauroyl peroxide in refluxing ethyl acetate (Scheme 3). The first product, isolated in 40% yield, proved to be open chain hydroxamate **17a**, arising through a radical Smiles rearrangement.[10] This ultimately leads to *N*-acetoxyamidyl radical **16**, which then abstracts a hydrogen atom from the solvent. The second product turned out to be

(6) For a review, see: El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.

(7) Oxley, P. W.; Adger, B. M.; Sasse, M. J.; Forth, M. A. *Org. Synth.* **1988**, *67*, 187.

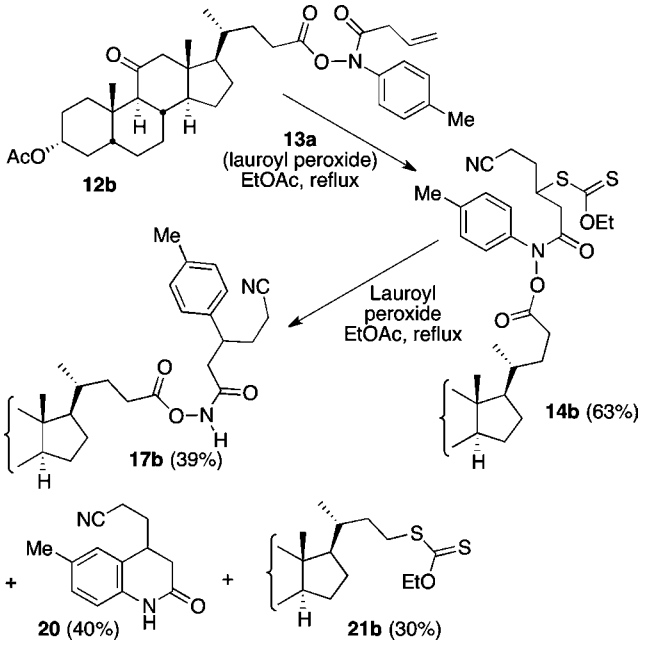
(8) In Schemes 3–5, placing lauroyl peroxide in parentheses indicates that it is used as the initiator in substoichiometric amounts. No parentheses means that the peroxide is used both as initiator and as a stoichiometric oxidant.

(9) (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719. (b) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671. (c) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Heterocycles* **2012**, *84*, 291.

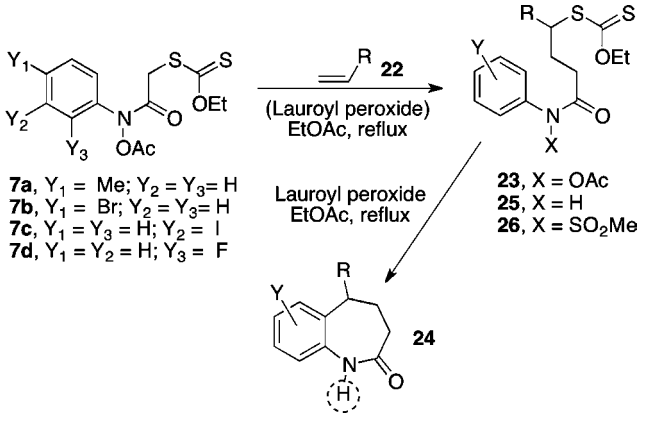
(10) (a) Studer, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: Weinheim, 2001; Vol. 2, 44. (b) Studer, A.; Bossart, M. *Tetrahedon* **2001**, *57*, 9649. (c) E. Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817.

dihydroquinolone **20**, obtained in 35% yield, where the acetoxy group of the hydroxamate moiety had been lost. As depicted in Scheme 3, the cyclization of radical **15** gives cyclohexadienyl radical **18**, which then undergoes β-scission of the weak N–O bond.[11] The acetyloxy radical thus produced evolves through rapid extrusion of carbon dioxide into a methyl radical, which can transfer a xanthate group from the starting material **14a** to give radical **15** and *S*-methyl xanthate **21a**.

Scheme 4



Scheme 5



Evidence for this mechanism was adduced by repeating the operation with steroid hydroxamate **14b**. As outlined in Scheme 4, the reaction furnished in the yields shown the expected open chain hydroxamate **17b** and dihydroquinolone

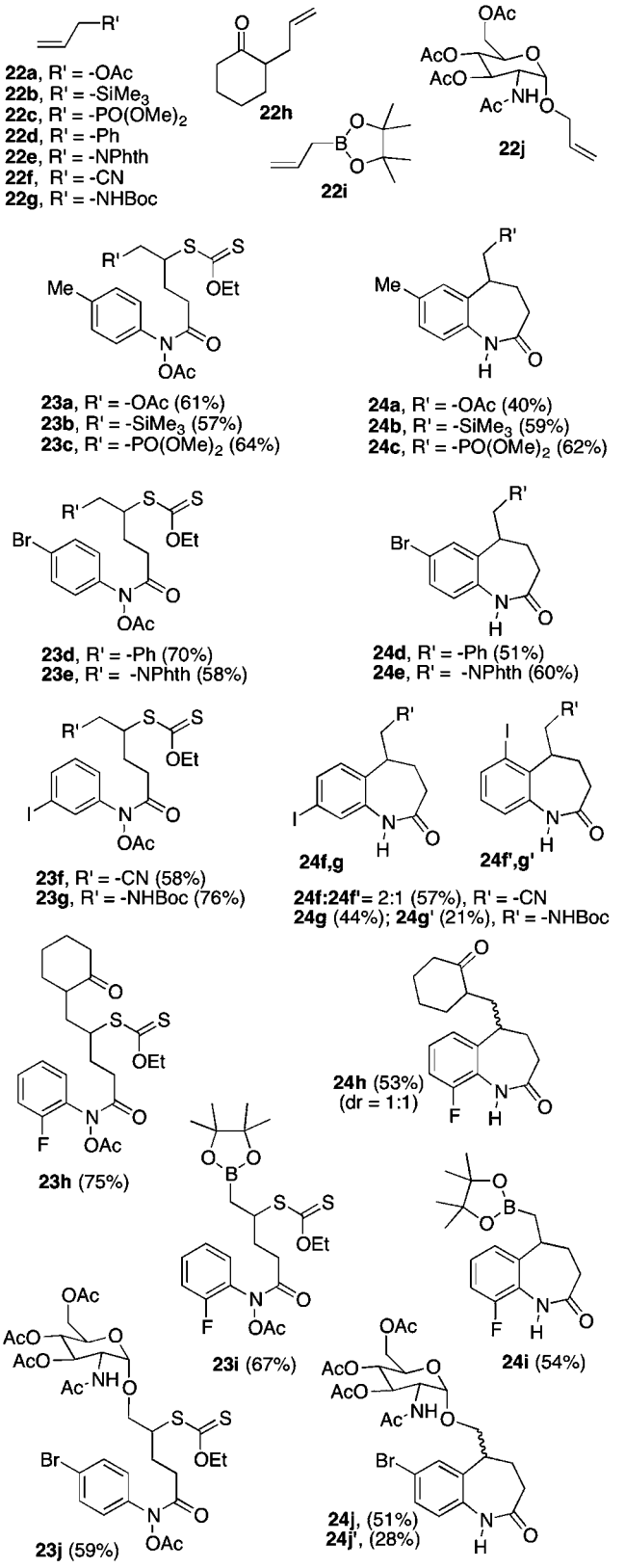


Figure 2. Examples of benzazepinones.

(11) Acyloxy radicals have been generated by treatment of *N*-acyloxyphthalimides with stannyl radicals. See: Barton, D. H. R.; Blundell, P.; Jaszberenyi, J. Cs. *Tetrahedron Lett*. **1989**, *30*, 2341.

20, in addition to steroid xanthate **21b**. Decarboxylation of the bile acid moiety had indeed taken place in accord with the mechanism displayed in Scheme 3. The fact that cyclization did proceed in the case of xanthates **14a** and **14b**, albeit in modest yield, encouraged us to examine the behavior of the even higher homologue **5**, $n = 2$. The cyclization in this case would lead to a benzazepinone **6**, $n = 2$. We had found in the past that it was possible in some cases to construct seven membered rings by direct radical cyclization onto aromatic or heteroaromatic rings. Furthermore, the observation that radicals **10** (Scheme 2) did not readily cyclize opened the possibility of their intermolecular capture by an alkene **22**, thus providing a direct and flexible access to xanthate precursors **23** needed for the formation of benzazepinones **24**, as indicated in Scheme 5.[9b,c,12]

The intermolecular addition to unhindered terminal alkenes indeed proved successful, as did the cyclization step. The examples assembled in Figure 2 give an idea of the scope and functional group tolerance of the process. No complications arising from a radical Smiles rearrangement were observed, in contrast to the lower analogous series. In this case, the Smiles rearrangement would have had to proceed through a temporary six-membered ring, which kinetically is a much slower process.

Thus, alkenes **22a**−**i** bearing a range of useful functional groups underwent the desired radical addition with xanthates **7a**−**d** to give new adduct xanthates **23a**−**i**, and these in turn were converted into benzazepinones **24a**−**i** in synthetically useful yields. Particularly noteworthy is the compatibility of the method with the presence of an aromatic bromide and, especially, iodide, as this allows further elaboration through the myriad transition metal catalyzed coupling reactions. The ring-closure in the presence of a *meta*-iodo substituent is only moderatly regioselective (2:1 in favor of a distal cyclization). In the case of **24f**/**24f′**, the two regioisomers could not be separated by chromatography, but a pure sample of the major isomer could be obtained by crystallization. Another interesting aspect is the ease of introducing a boronate (**24i**) or a complex carbohydrate motif (two separable epimers **24j** and **24j′**).

Direct access to *N*-unsubstituted benzazepinones cannot be accomplished by cyclization of secondary amide xanthates **25** (Scheme 5), presumably because of the relatively high rotation barrier and the predominance of the rotamer with a geometry unfavorable for ring-closure.[12,13] The best approach we have recently developed relies on methanesulfonamides of type **26** (Scheme 5), which give *N*-unsubstituted benzazepinones by extrusion of a methanesulfonyl radical, but high temperatures must be used in the cyclization step.[14]

The present convergent approach allies a flexibility in the choice of reacting partners with the simplicity and mildness of the experimental procedure. It constitutes a concise and cheap route to a class of highly privileged structures in medicinal chemistry.[15] Furthermore, the substitution pattern accessible by xanthate technology is not easily attained by more conventional synthetic methods.

Acknowledgment. We dedicate this paper with respect to the memory of Professor Robert E. Ireland (University of Virginia).[16] N.D.M.T. thanks Ecole Polytechnique for a scholarship.

Supporting Information Available. Experimental procedures, full spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) (a) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731. (b) Petit, L.; Botez, I.; Tizot, A.; Zard, S. Z. *Tetrahedron Lett.* **2012**, *53*, 3220.

(13) Yamasaki, R.; Tanatani, A.; Azumaya, I; Saito, S.; Yamaguchi, K.; Kagechika, H. *Org. Lett.* **2003**, *5*, 1265 and references cited therein.

(14) Charrier, N.; Liu, Z.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 2018.

(15) See for example: A. Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274.

(16) S.Z.Z. would like to put on record his debt to Prof. Ireland for being indirectly responsible for the discovery of a mild source of hydroxyl radicals: In the spring of 1989, I happened to be a visiting scholar at Texas A&M University when Bob Ireland was invited to give a seminar. During our brief meeting, he said he was interested in using the Barton decarboxylation reaction in one of his syntheses and asked if I could provide him with a reliable procedure for obtaining *N*-hydroxypyridine-2-thione from the commercial aqueous solution of its sodium salt. In those pre-internet days, I had to wait until I returned to France a couple of weeks later to retrieve the procedure from the thesis where it was detailed. I dutifully copied the procedure and decided to enclose a couple of grams of *N*-hydroxypyridine-2-thione, so that Bob Ireland's student would not have to wait to test the decarboxylation on his substrate. However, as I was about to place the sample in a small glassine envelope, Prof. Marcel Fétizon came by and we chatted at the door of my office. It was a grim and overcast day but, as we were chatting, the sun just came out for a few minutes and the sunlight struck the vial containing the *N*-hydroxypyridine-2-thione. When I eventually returned to my desk, I was dismayed to see that the nice off-white solid had turned into a brown goo on the side of the vial pointing towards the window. The initial irritation at the photochemical destruction of our main supply of the material soon gave way to curiosity, and we ultimately found that mere irradiation with a tungsten filament lamp of *N*-hydroxypyridine-2-thione resulted in the clean generation of hydroxyl radicals (Boivin, J.; Crépon, E.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 6869). This convenient source of hydroxyl radicals was later used by various research groups to cleave DNA strands.