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Application of Aryloximes as Solid-Phase Ketone Linkers

Salvatore D. Lepore[†] and Michael R. Wiley*

Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

wileymr@lilly.com

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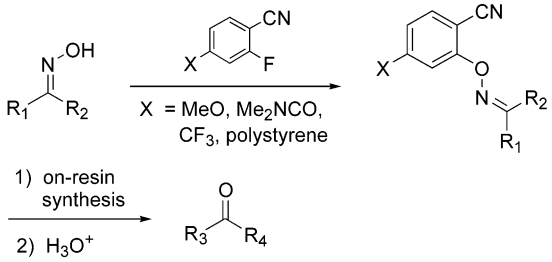
ABSTRACT



In both solution and the solid phase, a variety of ketone oxime anions have been treated with 4-substituted-2-fluorobenzonitriles to give the corresponding nucleophilic aromatic substitution aryloxime adducts. Under aqueous acidic conditions, these adducts underwent cyclization to give the corresponding ketones. Suzuki and amide coupling reactions were also successfully performed on two resin-bound oximes followed by subsequent cyclorelease to give ketone product in good yields and purities.

Techniques for the solid-phase synthesis of ketones have been limited to relatively few methods despite the presence of this funtional group in a large variety of pharmaceutical and natural products.[1] Ketones have been generated from the displacement of polymer-bound Weinreb amides with carbon nucleophiles.[2] More commonly, ketones have been prepared in solution and subsequently immobilized on a solid support through the use of a protecting group linker strategy.[3] Early work in this area produced linkers based on ketals,[4] thioketals,[5] and imines.[6] Webb's semicarbazide linker,[7] initially developed for the solid-phase synthesis of C-terminal peptide aldehydes, has been recently extended to the synthesis of trifluoromethyl ketones.[8] The linkage of ketones to polymer support as the hydrazone has also recently been described by Ellman.[9]

We became interested in developing an oxime-based ketone linker in the course of our investigations on the solid-phase synthesis of 3-aminobenzisoxazoles.[10,11] In this approach, based on the method of Shutske,[12] a ketone oxime[13] is coupled with a 2-fluorobenzonitrile to give an aryloxime intermediate (Scheme 1). Acidic hydrolysis then leads to cyclization of the aryloxime to produce the aromatic heterocycle and a ketone. In our earlier work, an oxime-

[†] Current address: Department of Chemistry, Florida Atlantic University, Boca Raton, FL 33431. E-mail: slepore@fau.edu.

(1) Over 100 ketone-containing drugs have been brought to market in the last 10 years according to the MDL Drug Data Report (electronic database).

(2) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Airey, J.; Labaudiniere, R. *J. Org. Chem.* **1999**, *64*, 1823. O'Donnell, M. J.; Drew, M. D.; Pottorf, R. S.; Scott, W. L. *J. Comb. Chem.* **2000**, *2*, 172.

(3) Backes, B. J.; Ellman, J. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 86.

(4) Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1973**, *51*, 3756.

(5) Huwe, C. M.; Künzer, H. *Tetrahedron Lett.* **1999**, *40*, 683.

(6) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221.

(7) Murphy, A. M.; Dagnino, R.; Vallar, P. L.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 3156.

(8) Poupart, M.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356. The Webb linker has also been recently used with nonfluorinated ketones; see: Giroux, A.; Han, Y. Solid-Phase Synthesis of Biaryl Aldehydes and Ketones Using Webb's Semicarbazide Linker. Book of Abstracts, 217th National Meeting of the American Chemical Society, Anaheim, CA, March 21−25, 1999; American Chemical Society: Washington, DC; 1999.

(9) Lee, A.; Huang, L.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 9907.

(10) Lepore, S. D.; Wiley, M. R. *J. Org. Chem.* **1999**, *64*, 4547.

(11) Lepore, S. D.; Wiley, M. R. *J. Org. Chem.* **2000**, *65*, 2924.

(12) Shutske, G. M.; Kapples, K. J. *J. Heterocycl. Chem.* **1989**, *26*, 1293.

(13) Aldehyde oximes were not studied since their corresponding aryloxime adducts are unstable to the basic conditions used in the SNAr reaction leading to the formation of nitriles; see: Cho, B. R.; Cho, N. S.; Song, K. N.; Kim, Y. K. *J. Org. Chem.* **1998**, *63*, 3006 and references therein.

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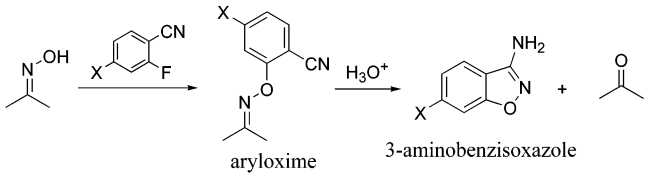
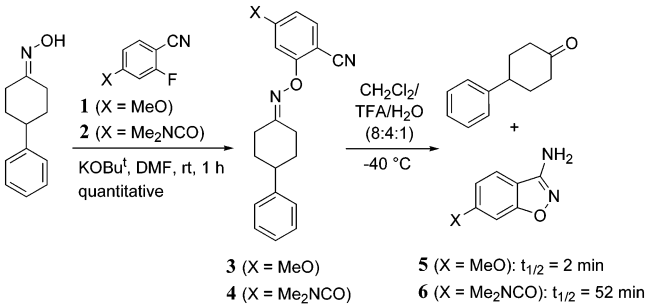
Scheme 1



containing resin[14] was employed so that this reaction sequence led to the cyclorelease of 3-aminobenzisoxazoles into solution. In our studies of this system, we observed that the rate of cyclization of the resin-bound aryloxime intermediate was very sensitive to the presence of electron-donating/withdrawing groups para to the nitrile. For example, in one case, an electron-donating group such as a *p*-methoxy accelerated the rate of cyclorelease by a factor of 100 relative to a *p*-bromo.[10] This observation presented an opportunity to address the major limitation to the use of oximes as latent ketone functional groups, namely, the forcing conditions required for oxime hydrolysis.[15] Thus, we envisioned attaching the arylnitrile component to polymer leading to a new resin-bound aryloxime intermediate. Treatment of this intermediate with aqueous acidic conditions would then liberate a ketone into solution leaving the 3-aminobenzisoxazole attached to the resin.

To further characterize the electronic dependence of the cyclization reaction in the solution-phase, compounds **3** and **4** were targeted. In addition to representing electron-donating and electron-withdrawing characteristics, we envisioned that solid-phase analogues of **3** and **4** could be readily synthesized for direct comparison with our solution-phase study. Thus, aryloximes **3** and **4** were prepared in near-quantitative yields[12] using 4-methoxy-2-fluorobenzonitrile (**1**) and 4-(dimethyl-aminocarbonyl)-2-fluorobenzonitrile (**2**) (Scheme 2).

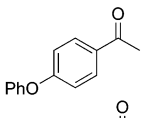
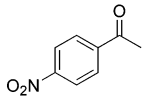
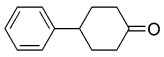
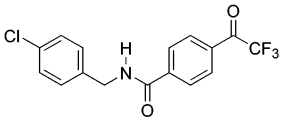
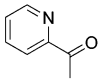
Scheme 2



Initially, adducts **3** and **4** were treated with 4:1 TFA/H_2O at room temperature leading to complete cyclization to give 4-phenylcyclohexanone and 3-aminobenzisoxazoles **5** and **6** in less than 1 min. However, the use of 8:4:1 CH_2Cl_2/TFA/H_2O at −40 °C revealed a significant rate difference. Under these conditions, adduct **3** underwent rapid cyclization to give the corresponding ketone ($t_{1/2}$ = 2 min) and 3-aminobenzisoxazole **5** (Scheme 2). In the case of the electron-deficient *N*,*N*-dimethylamido-benzonitrile adduct **4**, these conditions led to a significantly slower cyclization reaction ($t_{1/2}$ = 52 min).

Several additional ketone oximes[16] were reacted with arylnitrile **1** to give the corresponding aryloxime intermediates. Following solvent removal and aqueous workup, the aryloxime intermediates were then subjected to cyclization conditions followed by SCX purification.[17] The SCX column effectively removed **5** to give the corresponding ketones in >96% purity (Table 1). Ketones containing electron-donating and withdrawing groups (entries a and b) were obtained in good yields by treatment of the precursor aryloximes with

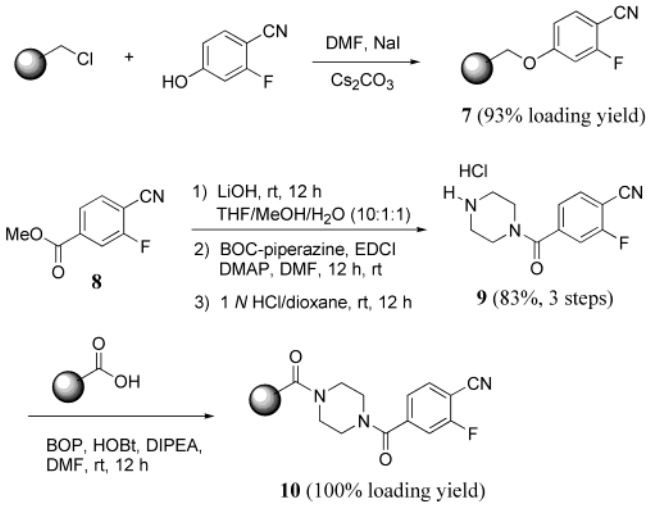
Table 1. Cyclization Yield of a Variety of Ketones Formed by the Aqueous Acidic Treatment of Their Precursor Aryloxime Adducts with **1** and Resins **7** and **10**

entry	ketone product	isolated yield[a] **1**[b]	**7**[c]	**10**[c]
a		95	86	83
b		81	65	77
c		89	88	75
d		74[d]	<5[e]	63[f]
e		0[g]	-	-

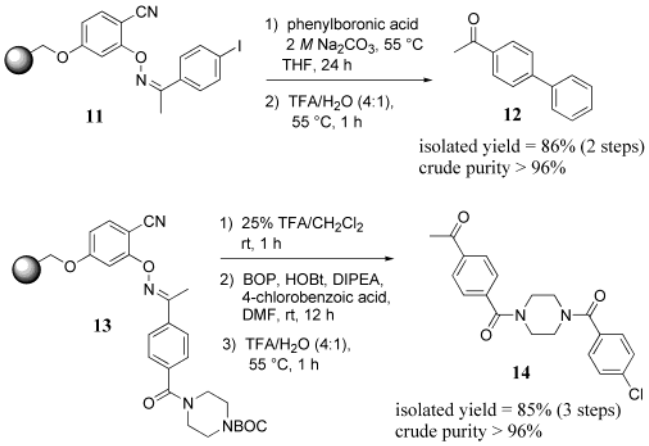
[a] All yields are after chromatography. For reactions with **1**, yields are for the two steps. For reactions with resins **7** and **10**, yields are based on loading, and the crude purities of the cyclorelease products are based on HPLC analysis and are >96% unless otherwise indicated. [b] Oximes were treated with KOtBu at room temperature in DMF followed by the addition of arylnitrile **1** and isolated by aqueous workup. Cyclization was performed at room temperature in 8:4:1 CH_2Cl_2/TFA/H_2O except in the case of entry d. [c] Oximes were treated with KOtBu at room temperature in DMSO and added to resin **7** or **10** suspended in THF and reacted for 4 h at 55 °C. Cyclorelease was performed at 55 °C in 4:1 TFA/H_2O for 1 h except in the case of entry d. [d] Cyclization was performed at 55 °C in 4:1 TFA/H_2O for 4 h. [e] Arylnitrile debenzylation of the resin gave the major side product. [f] Cyclorelease was performed at 55 °C in 4:1 TFA/H_2O for 12 h. [g] Only starting material was recovered.

(14) Degrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295.
(15) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1998; p 355.
(16) All oximes were prepared in near quantitative yields from the corresponding ketones by treatment with hydroxylamine hydrochloride (1.2 equiv) and pyridine (2.0 equiv) in refluxing ethanol.
(17) Aminobenisoxazole **5** was conveniently removed from the crude product mixture by filtration through an acidified SCX column. Interestingly, heterocycle **6** was not retained on the column. Presumably, the electron-donating character of the methoxy group in **5** increases the basicity of the 3-amine relative to **6**, allowing it to ionize on the SCX column.

Scheme 3



Scheme 4



8:4:1 CH_2Cl_2/TFA/H_2O for several hours at room temperature. Aliphatic ketones were also readily obtained under these conditions. For example, aryloxime **3** cyclized in less than 5 min to give 4-phenylcyclohexanone in 89% yield and >96% purity after SCX purification (entry c). To obtain trifluoromethyl ketone in reasonable yields (74%, two steps) from its corresponding aryloxime adduct, warming to 55 °C in 4:1 TFA/H_2O for 4 h was required (entry d). No deprotection was observed in the case of aryloxime-protected 2-acetylpyridine (entry e) even under forcing conditions of heat and concentrated aqueous TFA. For these reactions, starting material was recovered even after extended reaction times. The same was also true for both 3- and 4-acetylpyridine (not shown).

We then proceeded to prepare arylfluoride resins that were electronically similar to **1** and **2**. Arylfluoride resin **7** was prepared in *one step* by coupling Merrifield's resin[18] with 2-fluoro-4-hydroxy-benzonitrile. Both reagents are commercially available and relatively inexpensive.

Following the method of Hollinshead[19] (cesium carbonate and potassium iodide in DMF), the coupling reaction gave resin **7** in a 93% loading yield (0.96 mmol/g) (Scheme 3).[20] Electron-deficient arylnitrile resin **10** was prepared in four steps starting from 4-methoxycarbonyl-2-fluorobenzonitrile (**8**).[21] Methylester **8** was hydrolyzed to the corresponding acid by treatment with LiOH, in 10:1:1 THF/MeOH/H_2O at room temperature for 12 h (Scheme 3). The crude acid intermediate was then coupled to *N*-*tert*-butoxycarbonyl-piperazine using carbodiimide coupling conditions to give the corresponding piperazine amide. This amide was then treated with 1 N HCl in dioxane to give **9** as the HCl salt in 83% yield (three steps). Amine **9** was then coupled to carboxypolystyrene (1% cross-linked) to provide resin **10** in a near-quantitative loading yield (1.57 mmol/g) based on weight.[20]

Resins **7** and **10** were then treated with a variety of ketone oximes to give the resin-bound aryloxime intermediates in loading yields ranging from 50 to 80%. Interestingly, in the case of the 4-phenylcyclohexanone adduct with resins **7** and **10** (Table 1, entry c), treatment with 4:1 TFA/H_2O at room temperature led to very similar cyclorelease rates ($t_{1/2} \approx 45$ min).[22] At 55 °C under the same conditions, both aromatic and aliphatic ketones were recovered in reasonable yields and excellent purities after 1 h (Table 1, entries a−c) for both resins **7** and **10**. However, in the case of trifluoromethyl ketone (entry d), an extended reaction time of 12 h was necessary to effect the cyclorelease of the ketone from both resins. These more forcing conditions led to extensive cleavage of the arylnitrile moiety from the resin by a debenzylation reaction in resin **7**, whereas the more hydrolytically stable[23] resin **10** furnished the desired trifluoromethyl ketone product in 63% yield (based on loading) and >96% purity. Longer reaction times gave slightly improved yields but also led to decomposition products.

Having identified acceptable conditions for loading and cyclitive removal of a variety of substrates with resins **7** and **10**, we moved on to confirm the compatibility of the aryloxime linker with two widely used bond-forming reactions. Thus, aryliodide resin **11** was treated with phenylboronic acid under aqueous basic Suzuki coupling conditions[24] followed by cyclorelease to give the desired biaryl ketone **12** in 86% isolated yield (>96% purity) based on loading (Scheme 4).

Also, BOC-protected resin **13** was treated with 25% TFA/CH_2Cl_2 (1 h) followed by coupling to 4-chlorobenzoic acid

(18) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
(19) Hollinshead, S. P. *Tetrahedron Lett.* **1996**, *37*, 9157.
(20) Resin loading was based on weight. The near quantitative loading yield of resin **7** is also supported by yields based on elemental fluorine (98%) and nitrogen analysis (89%) ($n = 8$ in each case). For resin **10**, fluorine and nitrogen analysis gave 91% and 107% respectively. For resin **7**, a nitrile absorption at 2231 cm^{-1} is observed in the IR, and for resin **10**, this absorption occurs at 2237 cm^{-1}.
(21) Prepared in high yield from 4-bromo-2-fluorobenzonitrile by palladium-mediated methoxy carbonylation. Dufaud, V.; Thivolle-Cazat, J.; Basset, J. M. *J. Chem. Soc., Chem. Commun.* **1990**, 426.
(22) For a discussion of differences in the kinetics of solid- versus solution-phase reactions, see: Wang, S.; Foutch, G. L. *Biotechnol. Prog.* **1991**, *7*, 111. Chen, W. Y.; Foutch, G. L. *Chem. Eng. Sci.* **1989**, *44*, 2760.
(23) The treatment of resin **10** with TFA/H_2O at 55 °C for 24 h led to no appreciable decomposition.
(24) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177.

under typical benzotriazole activated-ester conditions to give the resin-bound amide (Scheme 4). The treatment of this resin intermediate with cyclorelease conditions led to an 85% isolated yield (>96% purity) of ketone **14**. The successful execution of both the Suzuki and amide coupling chemistry involving resins **11** and **13** is in agreement with our studies of a related system where we demonstrated that the aryloxime linker was compatible with a wide variety of bond-forming reaction conditions.[11]

In conclusion, we have developed a new solid-phase ketone linker based on the aryloxime functional group. Our model studies in the solution-phase have established that aryloxime groups such as **3** that contain electron-donating groups are more rapidly hydrolyzed to reveal the ketone than electron-deficient systems such as **4**. These solution-phase studies inspired the synthesis of analogous electron-rich and electron-deficient aryl oxime resins (oxime adducts of **7** and **10**). A variety of ketones including trifluoromethyl ketones were attached to both resins **7** and **10** via an aryloxime linkage. The ketones were then recovered in good yields and excellent purities (>96%). Suzuki and amide coupling reactions were also successfully performed on resin-bound ketones. On the basis of our findings, the aryloxime linker approach described in this report should find useful applications in the solid-phase synthesis of small-molecule ketone libraries.

Acknowledgment. The authors thank Prof. William Roush for helpful discussions and Ms. Jolyn Smith for the preparation of various intermediates used in this work.

Supporting Information Available: Experimental procedures and full characterization for compounds **9**, **12**, and **14** and resins **7** and **10** and a representative procedure for the addition of aryloxymes to resins **7** or **10** followed by subsequent cyclorelease. This material is available free of charge via the Internet at http://pubs.acs.org.

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