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A Novel Method for the Generation of Nitrile Oxides on Solid Phase: Application to the Synthesis of Substituted Benzopyranoisoxazoles

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ABSTRACT

A solid-phase synthesis of substituted benzopyranoisoxazoles is described. The six-step synthesis features a novel method of generating nitrile oxides on a polymer support followed by an intramolecular 1,3-dipolar cycloaddition with a tethered alkyne for assembly of the benzopyranoisoxazole scaffold. Furthermore, the utilization of single-bead attenuated total reflectance Fourier transform infrared (ATR-IR) microspectroscopy as an essential analytical tool for reaction optimization is highlighted.

Combinatorial chemistry and high throughput parallel synthesis have emerged as powerful tools for the generation of large collections of diverse compounds.[1] The pharmaceutical industry, in particular, has invested in and integrated numerous aspects of combinatorial chemistry into the drug discovery process with one goal being to provide novel ligands for the plethora of biological targets derived from the human genome.[2]

During the past decade, the quality of solid supports and linkers has improved significantly.[3] This, in turn, has expanded the number of synthetic transformations that can be successfully accomplished on solid phase and has led to an improvement in the purities and yields of the targeted compounds. Although numerous solid-phase chemistries have been reported in the literature, the majority are directed toward the solid-phase synthesis of heterocycles.[4] One strategy that has proven particularly valuable for the solid-phase synthesis of conformationally rigid heterocycles is the 1,3-dipolar cycloaddition reaction.[5] This strategy has been successfully applied to the solid-phase synthesis of maleimide-fused indolizinium carboxylates,[6] tricyclic tetrahydroquinolines,[7] tetrahydro-β-carbolines,[8] and indolyl diketopiperazine alkaloids.[9]

(1) For reviews on solid-phase synthesis see: (a) Bunin, B. A. *The Combinatorial Index*; Academic Press: New York, 1998. (b) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235. (c) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549. (d) Kingsbury, C. L. Mehrman, S. J.; Takacs, J. M. *Curr. Org. Chem.* **1999**, *3*, 497. (e) Corbett, J. W. *Org. Prep. Proced. Int.* **1998**, *30*, 489. (f) Booth, S.; Hermken, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1998**, *54*, 15385. (g) Nefzi, S.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449. (h) Hermken, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643. (i) Hermken, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *52*, 4527. (j) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (k) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

(2) Beeley, L. J.; Duckworth, D. M.; Southan, C. *Progress in Medicinal Chemistry* **2000**, 371.

(3) For reviews on solid-phase synthesis supports and linkers see: (a) Guiller, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. (b) Hudson, D. J. *J. Comb. Chem.* **1999**, *1*, 333. (c) Hudson, D. J. *J. Comb. Chem.* **1999**, *1*, 403.

(4) For a recent review: Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195.

(5) Kantorowski, E. J.; Kurth, M. J. *Mol. Diversity* **1997**, *2*, 207−216.

(6) Bicknell, A. J.; Hird, N. W.; Readshaw, S. A. *Tetrahedron Lett.* **1998**, *39*, 5869−5872.

(7) (a) Kiselyov, A. S.; Smith, L. II.; Virgilio, A.; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 7987−7996. (b) Kiselyov, A. S.; Smith, L. II.; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 5089.

(8) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291−1294.

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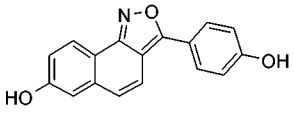
As a step toward identifying novel ligands for new biological targets, we also investigated the synthesis of conformationally rigid heterocyclic templates on solid phase. In particular, we were intrigued by a report[10] that the phenolic naphthoisoxazole ring system, exemplified by **1**, serves as a novel scaffold for the synthesis of estrogen receptor modulators. Thus, we speculated that the benzopyranoisoxazole ring system (**2**)[11] may serve as a novel steroid mimetic template, and herein we report the efficient solid-phase synthesis of substituted benzopyranoisoxazoles. The synthesis features a novel method of generating nitrile oxides on a polymer support under mild conditions followed by a subsequent intramolecular 1,3-dipolar cycloaddition with a tethered alkyne. Furthermore, we exemplify the utilization of single-bead attenuated total reflectance Fourier transform infrared (ATR-IR) microspectroscopy as an essential analytical tool for reaction optimization.[12]



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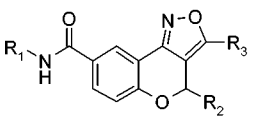

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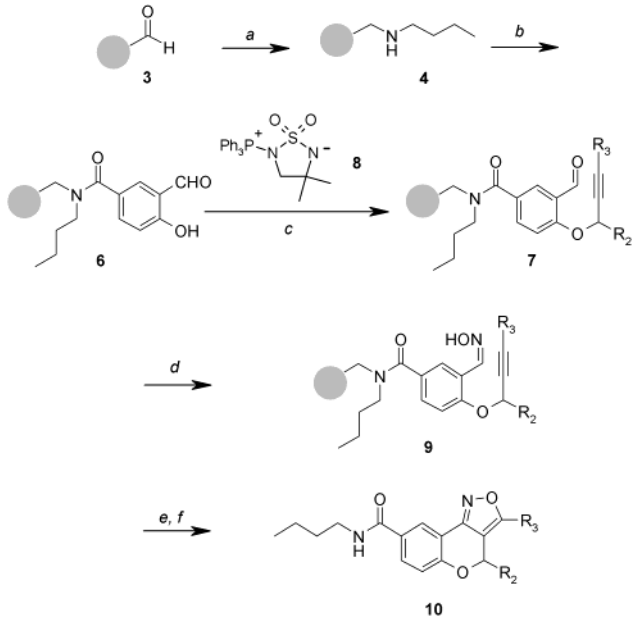
As a starting point, we chose 3-formyl-4-hydroxybenzoic acid as a properly functionalized starting material for the synthesis of our benzopyranoisoxazoles. The benzoic acid functionality would serve as a solid-phase attachment point via an amide linkage while the salicylaldehyde functionality contained key functionalities for elaboration of the pyranoisoxazole ring. Commercially available 2-(4-formyl-3-methoxyphenoxy)-ethyl polystyrene resin **3**[13] was treated with excess butylamine and sodium triacetoxyborohydride in 1,2-dichloroethane to give the corresponding amine-functionalized resin **4** (Scheme 1). The absence of a residual aldehyde following analysis by ATR-IR and magic angle spinning (MAS) ^{1}H NMR[14] demonstrated complete consumption of the resin-bound aldehyde. A number of standard conditions were evaluated for coupling of 3-formyl-4-hydroxybenzoic acid to the amine-functionalized resin; however, no conditions were identified that led to an acceptable yield or purity of the desired amide. Successful amide formation was realized in approximately 60% yield, as measured by differential ATR-IR, upon prior formation of the corresponding

Scheme 1. Solid-Phase Synthesis of Benzopyranoisoxazoles[a]



[a] Butylamine, $NaHB(OAc)_3$, DCE. [b] 3-Formyl-4-hydroxybenzoyl chloride (**5**), 2,6-lutidine, DCM. [c] (I) **8**, propargyl alcohol, DCM; (II) LiOH, H_2O, THF. [d] $H_2NOH\cdot HCl$, Et_3N, MeOH [e] NBS, Et_3N, DMF. [f] 15% TFA/DCM.

acid chloride (**5**) with thionyl chloride followed by addition to resin **4**. Fortunately, the unreacted resin-bound amine did not interfere with the remaining synthetic steps (vide infra). A small percentage (<5%) of ester formation was observed between resin-bound phenol and unreacted acid chloride; however, treatment with aqueous LiOH in 1,4-dioxane effected saponification of the ester to the desired phenol.

With the 3-formyl-4-hydroxybenzoyl moiety successfully loaded onto resin, our efforts focused on elaboration of the salicylaldehyde functionality to an aldoxime containing a phenol-tethered alkyne. Toward this end, subjection of the resin-bound phenol to a Mitsunobu reaction[15] by treatment with propargyl alcohol and DEAD or DIAD provided the propargyl ether **7**. A small amount of the resin was cleaved with 15% TFA in dichloromethane; however, several impurities were observed in the ^{1}H NMR spectrum with the major impurity derived from DEAD or DIAD. Variation of the solvent, temperature, and order of addition did not improve purity therefore alternative reagents were investigated. Several groups have reported that sulfonamide betaine **8** is an effective reagent for the solid-phase Mitsunobu reaction between a resin-bound phenol and an alcohol.[16] Exposure of **6** to a solution of propargyl alcohol and **8** in dichloromethane provided the desired product; however, several impurities were present following analysis of a cleaved (15% TFA/CH_2Cl_2) sample by LC/MS and ^{1}H NMR. As before,

(9) (a) Van Levezijn, A.; van Maarseveen, J. H.; Stegman, K.; Visser, G. M.; Kooman, G.-J. *Tetrahedron. Lett*. **1998**, *39*, 4737−4740. (b) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth. M. J. *J. Org. Chem*. **1998**, *63*, 3081−3086.

(10) Huebner, V. D.; Lin, X.; James, I.; Chen, L.; Desai, M.; Moore, J. C.; Krywult, B.; Navaratnam, T.; Singh, R.; Trainor, R.; Wang, L. WO 00/08001, **2000**.

(11) For solution-phase syntheses of the benzopyranoisoxazole skeleton see: (a) Sami, M.; Izhar; Kar; Gandhi, K.; Ray, Jayanata, K. *Org. Prep. Proced. Int.* **1991**, *23*, 186−8. (b) Fusco, R.; Garanti, L.; Zecchi, G. *Chim. Ind*. **1975**, *57*, 16. (c) Yoshimura, H.; Nagai, M.; Hibi, S.; Kikuchi, K.; Hishinuma, I.; Nagakawa, J.; Asada, M.; Miyamoto, N.; Hida, T.; et al. PCT Int. Appl. WO 9414777, 1994.

(12) Yan, B.; Gremlich, H.-U.; Moss, S.; Coppola, G. M.; Sun, Q.; Liu, L. *J. Comb. Chem*. **1999**, *1*, 46−54.

(13) Available from Novabiochem.

(14) Luo, Y.; Ouyang, X.; Armstrong, R. W.; Murphy, M. M. *J. Org. Chem*. **1998**, *63*, 8719−8722.

(15) (a) Devraj, R, *J. Org. Chem.* **1996**, *61*, 9368−9373. (b) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671.

(16) (a) Castro, J. L.; Matassa, V. G. *J. Org. Chem.* **1994**, *59*, 2289−2291. (b) Swayze, E. E. *Tetrahedron Lett.* **1997**, *38*, 8465−8468. (c) Brummond, K. M.; Lu, J. *J. Org. Chem*. **1999**, *65*, 1723−1726.

variation of the reaction conditions did not improve product purity. We hypothesized that exposure to TFA during the cleavage step led to a number of decomposition pathways due to the close proximity of the aldehyde and alkyne moieties. Thus, single-bead ATR-IR was investigated for on-bead reaction monitoring. In contrast to the post-cleavage data, ATR-IR indicated successful alkyl ether formation (Figure 1) in >90% yield. The shift in aldehyde C═O stretch

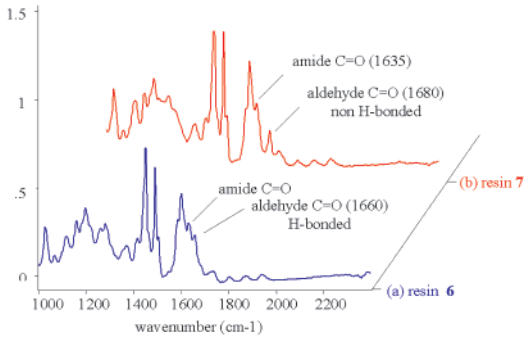


Figure 1. ATR-IR spectra are shown for the conversion of resin **6** to resin **7**.

from 1660 cm^{-1} in resin **6** to 1680 cm^{-1} in resin **7** was consistent with loss of an intramolecular hydrogen bond between the phenolic hydrogen and the aldehyde.[17] Formation of a propargylic hemiacetal was also observed in the IR spectrum (data not shown); however, resin washing with dilute acetic acid affected acetal hydrolysis to give resin **7**. Reaction with hydroxylamine hydrochloride and triethylamine in MeOH[18] afforded the desired aldoxime product **9**. As before, ATR-IR was essential for reaction monitoring due to competing hydrolysis of the aldoxime under the acidic conditions used for cleavage. Disappearance of the aldehyde C═O band accompanied by the appearance of bands diagnostic for an oxime functionality indicated successful oxime formation in >90% yield as measured by differential ATR-IR (Figure 2).

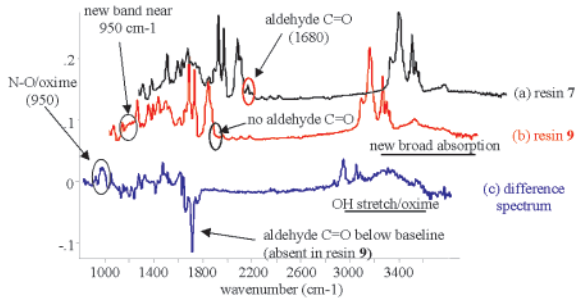
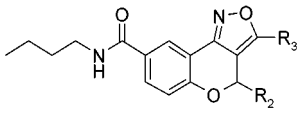


Figure 2. ATR-IR data are shown for (a) resin **7** and (b) resin **9**. The difference spectrum (**9** minus **7**) is included (see difference spectrum c) to highlight bands diagnostic for an oxime.

We next turned our attention to elaboration of **9** to a substituted benzopyranoisoxazole. Several groups have reported the generation of nitrile oxides from aldoximes on a solid phase. Of these, we were particularly attracted to the Huisgen method since this protocol is reported to give good yields and purities of products. Accordingly, treatment of resin-bound aldoxime **9** with excess commercially available bleach[19] in THF generated an intermediate nitrile oxide, which underwent spontaneous intramolecular 1,3-dipolar cycloaddition with the tethered alkyne to give the benzopyranoisoxazole ring system. While the desired product was evident by ^{1}H NMR, the aqueous bleach led to hydrolysis of the aldoxime and provided 10−15% of aldehyde **7** as a byproduct.[20] A number of other methods have been reported for the efficient conversion of aldoximes to nitrile oxides in solution including *N*-chlorobenzotriazole (NCBT),[21] iodobenzene dichloride,[22] lead tetraacetate,[23] and dehydrohalogenation of hydroximinoyl halide method.[24] We attempted a number of these reported methods on a solid phase with none providing an acceptable yield and purity of the desired product. Ultimately, it was discovered that treatment of **9** with a solution of NBS and triethylamine in DMF gave rise to the targeted benzopyranoisoxazole in 44% overall yield and 99% purity following cleavage and analysis of the crude product by LC/MS (Table 1, Entry 1), ^{1}H NMR, and ^{13}C

Table 1. Overall Yields and Purities of Substituted Benzopyranoisoxazoles **10a**−**i**[a,b]



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entry	product	R_2	R_3	overall yield (%)	purity (%)
1	**10a**	H	H	44	99
2	**10b**	Me	H	44	95
3	**10c**	Et	H	34	98
4	**10d**	*n*-Pr	H	55	99
5	**10e**	Ph	H	33	92
6	**10f**	H	Me	34	92
7	**10g**	H	$C_{10}H_{21}$	31	96
8	**10h**	H	Ph	37	99
9	**10i**	*i*-Pr	Ph	43	96

[a] Yields by gravimetric analysis based on isolated material following cleavage from a solid support. Yields were confirmed by Chemiluminescent Nitrogen Detection (CLND) and are ±10% of reported yields. [b] Purities based on LCMS analysis of cleaved samples. LCMS purity was consistent with purity by ^{1}H NMR.

NMR. Importantly there was no evidence of aldoxime hydrolysis in the crude product.

Once optimal conditions were identified for the efficient generation of the nitrile oxide on solid phase and subsequent

(17) For comparison, salicylaldehyde C═O stretch is 1660 cm^{-1} and *o*-anisaldehyde C═O stretch is 1685 cm^{-1}.

(18) Cheng, J.-F.; Mjalli, A. M. M. *Tetrahedron Lett.* **1998**, *39*, 939−942.

conversion to **10**, several substituted propargylic alcohols were selected to test the generality of the reaction. Nine substituted propargylic alcohols were loaded onto **6** using sulfonamide betaine **8** and converted to the corresponding aldoximes **9b**−**9i**. Subjection of each resin-bound aldoxime to NBS/Et_3N in DMF provided substituted benzopyranoisoxazoles **10b**−**10i** in 31−55% overall yield, as determined by gravimetric analysis and confirmed by Chemiluminescent Nitrogen Detection (CLND). While the modest yield (60%) of the amide formation step leads to modest overall yields, the remaining five transformations occur in >90% average yield and give rise to product purities ranging from 92 to 99% (Table 1). Substitution at the propargylic carbon with alkyl or aryl did not effect product purity, while substitution with aryl led to a decrease in product yield (Entry 9). In contrast, product yields were not effected by substitution with either an alkyl or aryl substituent at the terminal alkyne carbon. Similarly, simultaneous substitution at both the propargylic and the terminal alkyne carbons was not detrimental to product yield or purity. Overall, the efficient transformation of formyl resin **4** to substituted benzopyranoisoxazoles **10** is tolerant of various substitutions, and given the ease of synthesis of substituted and unsubstituted propargylic alcohols, incorporation of more functionalized monomers should proceed with ease.

In summary, we have demonstrated the efficient solid-phase synthesis of substituted benzopyranoisoxazoles in high yield and purity. The synthesis features very mild conditions for the generation of nitrile oxides from aldoximes on solid phase using NBS and Et_3N in DMF, which should be compatible with a number of solid-phase chemistries and monomer functionalities. We have also demonstrated the utility of ATR-IR as an essential tool for on-bead reaction monitoring and optimization. Given the large number of commercially available primary amines and propargylic alcohols, a diverse collection of substitituted benzopyranoisoxazoles can now be synthesized using the synthetic route described herein. Moreover, the resin-bound salicylaldehyde derivative **6** may serve as a generic template for the solid-phase synthesis of other steroid mimetic templates. These results will be reported in due course.

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Supporting Information Available: Experimental procedures for the research described in this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.
(20) In contrast see Kizer, D. E.; Miller, R. B.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 3535−3538.
(21) Kim, J. N.; Ryu, E. K. *Synth, Commun.* **1990**, *20*, 1373−1377.
(22) Radhakrishna, A. S.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1991**, *21*, 625−1629.
(23) Just, G.; Dahl, K. *Tetrahedron* **1968**, *24*, 5251.
(24) (a) Gruundmann, C.; Richer, R. J. *J. Org. Chem.* **1965**, *30*, 476. (b) Hassner, A.; Lokanatha, R. K. M. *Synthesis* **1989**, 57.