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Preparation of 4,5-Dihydronaphth[2,1-*c*] isoxazoles from Dilithiated 2-Tetralone Oxime and Select Esters

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Abstract: Dilithiated 2-tetralone oxime, prepared in excess lithium diisopropylamide, was condensed with aromatic esters, such as methyl 4-methoxybenzoate, followed by cyclization of the *C*-acylated intermediate with aqueous acid to give dihydronaphthisoxazoles, 4,5-dihydronaphth[2,1-*c*]isoxazoles.

Keywords: acylation–cyclization, dianion, dihydronaphthisoxazole, regioselectivity

INTRODUCTION

Isoxazoles and 4,5-dihydroisoxazoles constitute a very important group of heterocyclic compounds because of their use in other syntheses, their stand-alone potential with selectively bonded halogens and pendant groups, their interest for spectral and theoretical studies, and their biological and other application potential.[1]

There is ongoing interest in the methods of preparation of isoxazole and isoxazole-containing compounds. The condensation–cyclization of β-dicarbonyl compounds with hydroxylamine is one of the oldest and best documented synthetic methods, even though there is the probability for two

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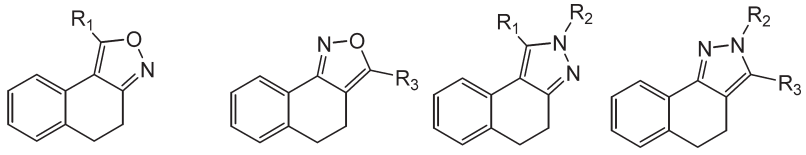
isomers forming when unsymmetrical β-dicarbonyl compounds are employed.[2] The preparations involving the 1,3-dipolar cycloaddition of nitrile oxides with alkenes or alkynes is usually regiospecific, and it is a leading method for the preparation of unsymmetrical 3,5-disubstituted isoxazoles and 4,5-dihydroisoxazoles (2-isoxazolines).[3] Another method initiated by the Hauser research group is always regiospecific, and it has been subsequently developed and expanded by others.[4] It involves 1,4-dilithiated oximes of $C(\alpha)$-aldehydes and ketones, which undergo condensation–cyclization with a variety of electrophilic reagents. The original account employed a variety of $C(\alpha)$-ketone oximes, such as those made from substituted acetophenones, 1-tetralone, deoxybenzoin, diphenylacetone, and cycloalkanones. These entry compounds were dilithiated with *n*-butyllithium at 0°C followed by a Claisen-type condensation with predominantly aromatic esters, then cyclization with dilute hydrochloric acid. The effective molar ratios of reagents were oxime/*n*-butyllithium/ester 1:2:0.5). Even though the yields of products were based on the ester, multigram quantities of products were readily obtained after recrystallization from common solvents. Other electrophilic reagents employed were aromatic carboxylic acid chlorides, which underwent di-*C*-acylation then cyclization to 4-acylisoxazoles,[5] diethyl oxalate to biisoxazoles,[6] and aromatic nitriles to also afford another regiospecific synthesis of unsymmetrical isoxazoles (oxime/*n*-butyllithium/nitrile 1:2:1).[7] The condensations with aromatic esters and nitriles are an unequivocal method for the preparation of 3,5-disubstuted unsymmetrical isoxazoles. The *C*-acylated precyclization intermediate formed during the condensation step (or condensation to an imine followed by hydrolysis to the ketone) has the five atoms in place that will make up the five-membered isoxazole ring. A single bond is formed during acid cyclization. Olofson et al. were able to improve the yields of select 5-alkylisoxazoles by lithiating the oxime with *n*-butyllithium at Dry Ice/acetone temperature −78°C or 0°C, followed by condensation–cyclization with *N,N*-dimethylcarboxylic acid amides, including dimethylformamide (DMF) and a couple of *N,N*-dimethylbenzamides (oxime/base/amide 1:2:1).[8] Because *N,N*-dimethylamides have the potential for lithiation of the *N*-methyl hydrogen, thus interfering with the reaction, Nitz et al. condensed-cyclized dilithiated oximes at 0°C with *N*-methoxy-*N*-methylalkylamides (oxime/*n*-butyllithium/amide 1:2:0.83)[9] to place an alkyl group in the 5-position of the isoxazole ring. Lithium diisopropylamide (LDA) used instead of *n*-butyllithium permitted a change in the ratio of the reagents (oxime/LDA/ester 1:3:1)[10] and increased the quantity of isoxazoles prepared where the yield is based on the oxime. The residual diisopropylamine resulting from the initial deprotonation process was easily removed during the workup. The trace amounts of diisopropylamine and THF that remained did not impede the crystallization of products from common solvents. This change in amount of and type of strong base resulted in additional oxime dianion-type investigations, involving an



4,5-Dihydronaphth-[2,1-*c*]isoxazoles | 4,5-Dihydronaphth-[1,2--*c*]isoxazoles | 4,5-Dihydro-2*H*-benz[*e*]indazoles | 4,5-Dihydro-2*H*-benz[*g*]indazoles

Figure 1. Fused-ring isoxazoles and pyrazoles.

abundance of readily available esters and related compounds such as carboxylic acid anhydrides, both general and specific.

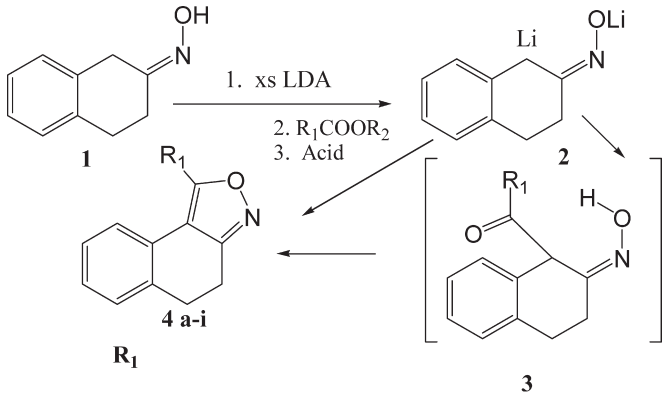
Although the preparation of substituted isoxazoles has been extensively investigated, there has been an expansion of these studies to include fused-ring isoxazoles. The fused-ring compounds germane to this report are illustrated in Fig. 1. They include 4,5-dihydronaphth[2,1-*c*]isoxazoles,[8] the focus of this investigation, and 4,5-dihydronaphth[1,2-*c*] isoxazoles prepared by others.[11]

Some of our specific projects have focused on 1- and 2-tetralone oximes and hydrazones because of their applications for ligand preparations and biological studies, especially in agriculture. The synthons using dilithiated 1-tetralone oximes and esters for the preparation of 4,5-dihydronaphth[1,2-*c*]isoxazoles were very straightforward,[12] along with projects involving dilithiated 1-tetralone phenylhydrazones or carboalkoxyhydrazones[13] with esters for the preparation of 4,5-dihydro-2*H*-benz[*g*]indazoles (Fig. 1). The preparations of 4,5-dihydro-2*H*-benz[*e*]indazoles involving condensation–cyclization of dilithiated 2-tetralone phenylhydrazone[14] or carbomethoxyhydrazones[15] with aromatic esters were more challenging, yet successful, but resulted in lower yields for 4,5-dihydrobenz[*e*]indazoles (Fig. 1) in direct comparison to analogous compounds prepared from 1-tetralone hydrazones.

The use of dilithiated 2-tetralone oxime **1** has proven to be the greatest challenge regarding condensations with certain electrophilic reagents. Nitz et al. were unable to condense dilithiated 2-tetralone oxime **2** and diphenylacetone oximes with the specialty amides,[9] but Hoskin and Olofson were successful with the condensation of dilithiated 2-tetralone oxime **2** with a more electrophilic carbocation salt solution made from trifluoromethanesulfonic acid and DMF, which resulted in the first and apparently only example of a 4,5-dihydronaphth[2,1-*c*]isoxazole.[8] They attributed these results to diminished reactivity of these stabilized dianions (intermediate 2, Scheme 1).

RESULTS AND DISCUSSION

During the current investigation, 2-tetralone oxime **1** was dilithiated to **2** with excess LDA, which was followed by condensation with select aromatic esters to give *C*-acylated intermediates **3**, which were not isolated but cyclized



4a. 3,4,5-$(CH_3O_3)C_6H_2$-
4b. 3,4-$(CH_3O)_2C_6H_3$-
4c. 4-$CH_3OC_6H_4$-
4d. 4-HOC_6H_4-
4e. 4-IC_6H_4-
4f. 4-BrC_6H_4-
4g. 4-ClC_6H_4-
4h. 3-ClC_6H_4-
4i. 4-$CH_3C_6H_4$-

R_2 = ethyl or methyl

Scheme 1. 4,5-Dihydronaphth[2,1-*c*]isoxazoles.

directly with aqueous hydrochloric acid to afford all-new fused-ring 4,5-dihydronaphth[2,1-*c*]isoxazoles **4a**–**i**. Dihydronaphthisoxazoles **4a**–**i** were prepared in 14–64% yield, with an average yield of 34%. Even with the lower yield products, multigram quantities of them can be prepared after modest scale up followed by routine recrystallization. The yields **4a**–**i** may be attributed to several factors in addition to a less reactive or unreactive carbanion–enolate type system, **2**. Also, 2-tetralone oxime is more challenging to prepare, and it is less stable than 1-tetralone oxime. The varying stability of this entry compound plus varied challenges in handling probably have an effect on the overall yield of products. The success of these reactions is apparently due to the choice of base, LDA. Diisopropylamine resulting from the twofold deprotonation of oximes with LDA is available for coordination with lithium of the multiple anion-type system and/or resulting intermediates involved in the condensation process, which is not the situation with *n*-butyllithium alone. Even though aromatic esters are not especially reactive electrophilic reagents, the combination of LDA/THF at 0°C for dilithiation gives an active enough 1,4-dianion-type system to condense with them. Our investigations with tetramethylethylenediamine (TMEDA) with this dianion-type system have been limited, and we did not detect any benefit from its use. Also, the characterization of each product was straightforward, with no anomalies.

CONCLUSIONS

Every compound prepared and reported here is new, and they may be difficult to prepare by other routes or procedures. They are an initial part of the synthons of a less-known group of fused-ring isoxazoles that have potential for overall continued study and development. The general reaction sequence from 2-tetralone to the product may not represent optimal conditions for the preparation of a particular dihydronaphthisoxazole, but multigram quantities of readily purified product can be obtained.

EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting-point apparatus in open capillary tubes and are uncorrected. FT-IR spectra were obtained with a Nicolet Impact 410 FT-IR or a Mattson Genesis II FT-IR with Specac Golden Gate Accessory. NMR spectra were obtained with a Varian Associates Mercury Oxford spectrometer, 300 MHz for ^{1}H and 75 MHz for ^{13}C, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Combustion analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ.

General Procedure for Preparation of 4,5-Dihydronaphth[2,1-*c*]isoxazoles (4a–i)

(Ratio of reagents: oxime/LDA/ester 1:3:1; for **4d**, 1:4:1.) In a typical reaction sequence, LDA (0.048 mol) was prepared by the addition of 30 mL (or 40.0 mL for **4d**) of 1.6 M *n*-butyllithium (0.048 mol or 0.063 mol for **4d**) to a three-neck, round-bottomed flask (e.g., 500 mL), equipped with a nitrogen inlet tube, a side-arm addition funnel (e.g., 125 mL), and a magnetic stir bar. The flask was cooled in an ice bath, and 4.88 g (or 6.41 g for **4d**) (0.048 mol or 0.063 mol for **4d**) of diisopropylamine (Aldrich Chem. Co., 99.5%), dissolved in 25–30 mL of dry tetrahydrofuran (THF) (sodium/benzophenone–ketyl), was added from the addition funnel at a fast dropwise rate during 5 min (0°C, N_2). The solution was stirred at 0°C for an additional 15–20 min and then treated via the addition funnel with 2.42 g (0.0150 mol) of 2-tetralone oxime dissolved in 35–45 mL of THF. The addition time was 5 min. After 45–60 min of dilithiation at 0°C, 0.0158 mol of ester, dissolved in 25–35 mL of THF, was added to the dilithiated intermediate, and the solution was stirred for 1–1.5 h (0°C, N_2). Finally, 100 mL of 3 M hydrochloric acid was added, and the two-phase mixture was well stirred and heated under reflux for 30–45 min. At the end of this period, the mixture was poured into a large flask containing ice (ca. 100 g) followed by 100 mL of solvent-grade ether. The mixture was then

neutralized with solid sodium bicarbonate, and the layers were separated. The aqueous layer was extracted with ether (2 × 75 mL), and the organic fractions were combined, evaporated, and recrystallized.

Data

1-(3,4,5-Trimethoxy)phenyl-4,5-dihydronaphth[2,1-*c*]isoxazole (**4a**)

Condensation–cyclization of **2** with methyl 3,4,5-trimethoxybenzoate afforded **4a**, (3.24 g, 64% yield), mp 125–127°C (methanol): IR, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.97–3.04 (m. 4H, CH_2CH_2), 3.86 (s, 6H, OCH_3), 3.94 (s, 3H, OCH_3), 7.05 (s, 2H, ArH), 7.17–7.21, 7.22–7.32, and 7.69–7.72 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$) δ ppm 21.3, 29.6, 56.5, 61.3, 105.1, 111.5, 123.9, 124.6, 127.0, 128.0, 129.2, 136.4, 139.8, 153.7, 162.8, and 163.1. Anal. calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.67; N, 4.15. Found: C, 71.20; H, 5.66:, N, 4.07.

1-(3,4-Dimethoxyphenyl)-4,5-dihydronaphth[2,1-*c*]isoxazole (**4b**)

Condensation–cyclization of **2** with methyl 3,4-dimethoxybenzoate afforded **4b** (1.72 g, 36% yield), mp 129–131°C (methanol): IR, 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.96–3.03 (m. 4H, CH_2CH_2), 3.89 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.96–6.99, 7.15–7.31, 7.40–7.44, 7.64–7.67 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$) δ ppm 21.3, 29.7, 56.2, 56.3, 110.7, 111.0, 111.4, 121.0, 121.3, 124.3, 127.1, 127.7, 128.2, 129.1, 136.3, 149.3, 150.8, and 163.0. Anal. calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.57; N, 4.56. Found: C, 74.17; H, 5.61; N, 4.46.

1-(4-Methoxyphenyl)-4,5-dihydronaphth[2,1-*c*]isoxazole (**4c**)

Condensation–cyclization of **2** with methyl 4-methoxybenzoate afforded **4c** (1.16 g, 28% yield), mp 111–114°C (methanol): IR, 1604 cm^{-1}; ^1H, NMR ($CDCl_3$) δ ppm 2.97–3.01 (m. 2H, CH_2), 3.72 (m, 2H, CH_2), 3.88 (s, 3H, OCH_3), 7.00–7.03, 7.17–7.26, 7.58, 7.73–7.76 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ ppm 21.3, 29.7, 55.6, 110.9, 114.5, 121.2, 124.2, 127.2, 127.6, 128.2, 129.0, 129.5, 136.2, 161.3, and 163.1. Anal. calcd. for $C_{18}H_{15}NO_2$: C, 77.95; H, 5.45; N, 5.05. Found: C, 77.86; H, 5.56; N, 4.89.

1-(4-Hydroxyphenyl)-4,5-dihydronaphth[2,1-*c*]isoxazole (**4d**)

Condensation–cyclization of **2** with lithium methyl 4-hydroxybenzoate afforded **4d** (0.553 g, 14% yield), mp 246–249°C (methanol): IR, 3100, 1626 cm^{-1}; ^1H NMR (DMSO-d_6) δ ppm 2.87–3.01 (m, 4H, CH_2CH_2), 6.94–6.96, 7.17–7.60 (m, 8H, ArH), and 10.16 (s, 1H, ArOH); ^{13}C NMR

($CDCl_3$) δ ppm 21.1, 29.0, 110.5, 116.6, 119.1, 123.9, 127.6, 127.9, 128.1, 129.6, 129.9, 136.5, 160.5, 162.8, and 163.3. Anal. calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.38; H, 5.05; N, 5.13.

1-(4-Iodophenyl)-4,5-dihydronaphth[2,1-*c*]isoxazole (**4e**)

Condensation–cyclization of **2** with ethyl 4-iodobenzoate afforded **4e** (2.30 g, 41% yield), mp 124–126°C (methanol): IR, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.87–3.03 (m, 4H, CH_2CH_2), 7.09–7.26 (m, 3H, ArH), 7.47–7.50 (m, 3H, ArH), 7.77 (d, 2H, ArH, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ ppm 20.8, 29.2, 96.6, 111.9, 123.9, 126.9, 127.2, 127.7, 127.8, 128.8, 129.0, 135.0, 138.9, 161.3, and 162.8. Anal. calcd. for $C_{17}H_{12}INO$: C, 54.72; H, 3.24; N, 3.75. Found: C, 54.95; H, 3.18; N, 3.58.

1-(4-Bromophenyl)-4,5-dihydronaphth[2,1-*c*]isoxazoles (**4f**)

Condensation–cyclization of **2** with ethyl 4-bromobenzoate afforded **4f** (1.42 g, 29% yield), mp 117–120°C (methanol): IR, 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.97–3.01 (m, 4H, CH_2CH_2), 7.27–7.29, 7.62–7.70 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ ppm 21.2, 29.5, 112.2, 124.8, 127.2, 127.5, 127.6, 128.0, 128.1, 129.1, 129.5, 132.2, 132.6, 136.4, and 163.1. Anal. calcd. for $C_{17}H_{12}BrNO$: C, 62.60; H, 3.71; N, 4.29. Found: C, 62.98; H, 3.64; N, 4.01.

1-(4-Chlorophenyl)-4,5-dihydronaphth[2,1-*c*]isoxazoles (**4g**)

Condensation–cyclization of **2** with methyl 4-chlorobenzoate afforded **4g** (1.99 g, 47% yield), mp 116–118°C (methanol): IR, 1636 cm^{-1}; ^1H, NMR ($CDCl_3$) δ ppm 2.98–3.07 (m, 4H, CH_2CH_2), 7.23–7.31, 7.47–7.54, 7.75–7.78 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ ppm 21.2, 29.6, 112.1, 124.2, 127.2, 127.3, 127.6, 128.0, 129.1, 129.2, 129.5, 136.4, 136.5, 161.7, and 163.1. Anal. calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.25; H, 4.39; N, 4.67.

1-(3-Chlorophenyl)-4,5-dihydronaphth[2,1-*c*]isoxazoles (**4h**)

Condensation–cyclization of **2** with methyl 3-chlorobenzoate afforded **4h** (1.10 g, 26% yield), mp 91–94°C (methanol): IR, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.95–3.06 (m, 4H, CH_2CH_2), 7.16–7.81 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ ppm 21.2, 29.6, 112.5, 124.4, 126.0, 127.4, 127.5, 127.9, 128.0, 128.2, 130.5, 130.6, 135.2, 136.4, 161.3, and 163.1. Anal. calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.35; H, 4.29; N, 4.92.

1-(4-Methylphenyl)-4,5-dihydronaphth[2,1-*c*]isoxazoles (**4i**)

Condensation–cyclization of **2** with methyl 4-methylbenzoate afforded **4i** (0.982 g, 25% yield), mp 122–125°C (methanol): IR, 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 2.44 (s, 3H, CH_3), 2.98–3.01 (m, 4H, CH_2CH_2), 7.17–7.31, 7.68–7.71 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ ppm 21.2, 21.7, 29.6, 111.4, 125.8, 127.0, 127.6, 127.9, 128.0, 129.0, 129.8, 136.2, 140.7, and 162.9. Anal. calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 80.50: H, 5.39; N, 4.51.

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