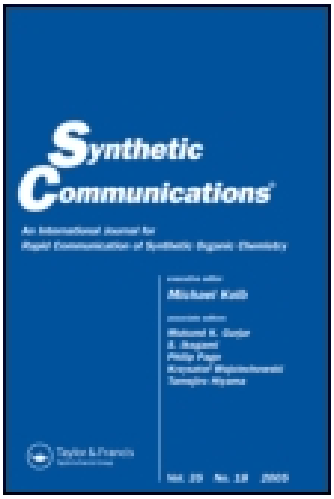


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Simple Strategy for the Preparation of 6-Substituted 3H-Benzoxazol-2-ones and 3H-Benzothiazol-2-ones

Russell J. DeOrazio [a], Jun-Ho Maeng [a], David D. Manning [a], Brian A. Sherer [a], Ian L. Scott [a] & Sham S. Nikam [b]

[a] AMRI, Albany, New York, USA

[b] Pfizer Inc., Ann Arbor, Michigan, USA

Accepted author version posted online: 30 Jun 2011.Published online: 09 Jun 2011.

To cite this article: Russell J. DeOrazio, Jun-Ho Maeng, David D. Manning, Brian A. Sherer, Ian L. Scott & Sham S. Nikam (2011) A Simple Strategy for the Preparation of 6-Substituted 3H-Benzoxazol-2-ones and 3H-Benzothiazol-2-ones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:23, 3551-3555, DOI: 10.1080/00397911.2010.519093

To link to this article: http://dx.doi.org/10.1080/00397911.2010.519093

Synthetic Communications®, 41: 3551–3555, 2011

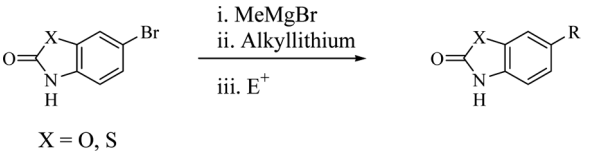
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.519093

Taylor & Francis
Taylor & Francis Group

A SIMPLE STRATEGY FOR THE PREPARATION OF 6-SUBSTITUTED 3*H*-BENZOXAZOL-2-ONES AND 3*H*-BENZOTHIAZOL-2-ONES

Russell J. DeOrazio,[1] Jun-Ho Maeng,[1] David D. Manning,[1] Brian A. Sherer,[1] Ian L. Scott,[1] and Sham S. Nikam[2]
[1]*AMRI, Albany, New York, USA*
[2]*Pfizer Inc., Ann Arbor, Michigan, USA*

GRAPHICAL ABSTRACT



X = O, S

Abstract *The double metallation of 6-bromo-3*H*-benzothiazol-2-one and 6-bromo-3*H*-benzoxazol-2-one with methyl magnesium bromide and alkyllithium bases is described. Alkylation with a variety of electrophiles occurs at the 6-position of the heterocycles in good yields.*

Keywords Benzothiazolidinone; benzoxazolidinone; metallation

INTRODUCTION

Our efforts to generate subtype-selective NR1a/2B NMDA (*N*-methyl-D-aspartate) receptor antagonists[1] prompted us to investigate synthetic methods that allow for substitution at the 6-position of benzoxazolidinone and benzothiazolidinone heterocycles. Previous work by other investigators has primarily relied on Friedel–Crafts acylation methodology or strategies that require protection of the heterocyclic nitrogen, and these were not suitable for our needs.[2–6]

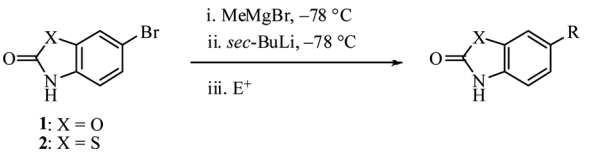
We have developed a simple method (Scheme 1) to prepare 6-substituted benzoxolidinones by the double metallation of unprotected bromides **1** and **2**.[7,8]

RESULTS AND DISCUSSION

Initially, we sought to activate bromide **1** toward reaction with carbon electrophiles by preparing the dianion using alkyllithium bases. Treatment of **1** with 2 equivalents of *sec*-butyllithium followed by subsequent reaction with 1,4-cyclohexanedione

Received March 10, 2010.

Address correspondence to David D. Manning, Discovery R&D Chemistry, AMRI, 26 Corporate Circle, P. O. Box 15098, Albany, NY 12212-15098, USA. E-mail: David.Manning@amriglobal.com



1: X = O
2: X = S

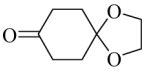
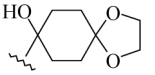
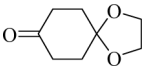
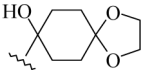
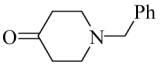
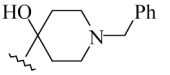
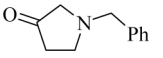
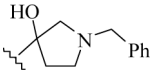
Scheme 1. Preparation of 6-substituted benzoxazolidinones and benzothiazolidinones.

mono-ethylene ketal did not provide any of the desired addition product. Protection of the heterocyclic nitrogen with a benzyl group followed by attempted metallation with *sec*-butyllithium was unsuccessful because of benzylic deprotonation. Faced with these two results, we hypothesized that the selection of an appropriate base may allow for selective deprotonation of the heterocyclic nitrogen. Subsequent transmetallation with an alkyllithium should give a doubly differentiated metallated intermediate that would presumably react at the 6-postion with electrophiles.

To test our hypothesis, we chose to formylate heterocycles **1** and **2**; the corresponding aldehydes were key intermediates for our program, and the preferred electrophile, dimethylformamide, was expected to be sufficiently reactive under the reaction conditions. Our results are shown in Table 1.

Treatment of a suspension of bromide **1** in tetrahydrofuran with methyl magnesium bromide at −78 °C resulted in deprotonation of the heterocyclic nitrogen as evidenced by off-gassing of methane. Subsequent addition of 2 equivalents of *tert*-butyllithium at −78 °C generated a thick white suspension. Dimethylformamide was added to the cold reaction mixture, and after warming to room temperature, the reaction was quenched with water. Following workup, the aldehyde was obtained in a moderate yield and was contaminated with unreacted bromide **1**. We found that the magnesium species of **1** could be titrated with *tert*-butyllithium to give a bright yellow solution upon complete consumption of the bromide. Aldehyde of good yield and purity could be obtained using this protocol. No further purification of the product aldehyde was necessary. Application of this methodology to benzothiazolidinone **2** was equally successful.

Table 1. 6-Substituted benzoxazolidinones and benzothiazolidinones

Entry	Substrate	E^+	R	Yield (%)
1	**1**	DMF[a]	CHO	81
2	**2**	DMF[a]	CHO	96
3	**1**			57
4	**2**			54
5	**1**			69
6	**1**			51

[a]*tert*-Butyl lithium was used instead of *sec*-butyl lithium for step ii, Scheme 1.

This methodology is also applicable to ketones (Table 1, entries 3–6). The yields are somewhat less than those from the formylation reaction and may be attributed to enolization of the ketone.

In conclusion, we have developed a useful method for the preparation of 6-substituted benzoxazolidinone and benzothiazolidinone heterocycles. The 6-carboxaldehydes (Table 1, entries 1 and 2) are anticipated to be of general interest as useful synthetic intermediates.

EXPERIMENTAL

Proton NMR spectra were obtained at 300 MHz on a Bruker AC 300 spectrometer and at 500 MHz on a Bruker AMX 500 spectrometer using tetramethylsilane as an internal reference. Melting points were determined using a Mel-Temp II melting-point apparatus and are uncorrected. Mass spectra were obtained on a Varian 1200L quadrupole MS (ESI). Elemental analyses were performed by Intertek QTI in Whitehouse, N.J., USA. Compound **1** was prepared according to literature protocol,[9] and compound **2** was purchased from Aldrich.

Procedure A: Formylation of Bromide 1

To a −78 °C solution of **1** (20.0 g, 93.4 mmol) in tetrahydrofuran (THF, 180 mL) was added MeMgBr (34.5 mL of a 3.0 M solution in diethyl ether, 103 mmol). After 45 min, anhydrous THF (750 mL) was added at a rate that maintained the internal reaction temperature below a threshold of −50 °C. After the solution returned to −78°C, *tert*-butyl lithium (200 mL of a 1.7 M solution in pentane, 196 mmol) was added dropwise. After 15 min, DMF (44 mL, 561 mmol) was added to the yellow mixture, and the cold bath was removed. After 2 h, the reaction was quenched with water, and the THF was removed under reduced pressure. The residue was partitioned between EtOAc and 1 N HCl. The aqueous layer was extracted with EtOAc (2×). The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. Precipitation from hexanes/EtOAc gave 2-oxo-2,3-dihydrobenzoxazole-6-carboxaldehyde (12.4 g, 81%) as an off-white solid: mp 208–209 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.13 (s, 1H), 9.92 (s, 1H), 7.78 (d, $J = 8$ Hz, 1H), 7.75 (s, 1H), 7.29 (d, $J = 8$ Hz, 1H); ESI MS m/z 164 $[M+H]^+$. Anal. calcd. for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.64; H, 2.97; N, 8.54.

2-Oxo-2,3-dihydrobenzothiazole-6-carboxaldehyde

Following procedure A, bromide **2** was transformed into the corresponding aldehyde (3.74 g, 96%), which was isolated as a white solid: mp 227–228 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.39 (s, 1H), 9.90 (s, 1H), 8.17 (d, $J = 1$ Hz, 1H), 7.85 (dd, $J = 8$, 1 Hz, 1H), 7.30 (d, $J = 8$ Hz, 1H); ESI MS m/z 180 $[M+H]^+$. Anal. calcd. for $C_8H_5NO_2S{\cdot}0.1H_2O$: C, 53.09; H, 2.90; N, 7.74. Found: C, 53.14; H, 3.10; N, 7.37.

Procedure B: Alkylation of Ketone Substrates

Bromide **1** (1.50 g, 7.00 mmol) was dissolved in anhydrous THF (45 mL), and the solution was cooled to −78 °C. Solutions of MeMgBr (2.60 mL of a 3.0 M

solution in Et_2O, 7.70 mmol), *sec*-BuLi (5.90 mL of a 1.3 M solution in cyclohexane, 7.70 mmol), and 1,4-cyclohexanedione *mono*-ethylene ketal (1.30 g, 8.40 mmol) in anhydrous THF (10 mL) were added sequentially at 30-min intervals. After the final addition, the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of saturated NH_4Cl (20 mL). The reaction mixture was diluted with EtOAc (200 mL), washed with saturated NaCl (100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 1:1 hexanes/EtOAc to 1:3 hexanes/EtOAc) gave 6-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-3*H*-benzoxazol-2-one (1.16 g, 57%) as a white foam: mp 185–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.52 (s, 1H), 7.34 (s, 1H), 7.23 (dd, $J = 8$, 1 Hz, 1H), 7.02 (d, $J = 8$ Hz, 1H), 4.98 (s, 1H), 3.88 (s, 4H), 1.99–1.86 (m, 4H), 1.65–1.52 (m, 4H); ESI MS m/z 292 $[M+H]^+$. Anal. calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.55; H, 6.10; N, 4.85.

6-(8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-3*H*-benzothiazol-2-one

Following procedure B, bromide **2** was metallated and then condensed with 1,4-cyclohexanedione *mono*-ethylene ketal. Purification of the crude product by flash chromatography (silica, 1:1 to 1:2 hexanes/EtOAc) gave the alcohol (1.81 g, 54%) as a white foam: mp 196–197 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.78 (s, 1H), 7.63 (s, 1H), 7.35 (d, $J = 8$ Hz, 1H), 7.05 (d, $J = 8$ Hz, 1H), 4.93 (s, 1H), 3.88 (s, 4H), 2.07–1.87 (m, 4H), 1.69–1.47 (m, 4H); ESI MS m/z 308 $[M+H]^+$. Anal. calcd. for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56. Found: C, 58.58; H, 5.64; N, 4.54.

6-(1-Benzyl-4-hydroxypiperidin-4-yl)-3*H*-benzoxazol-2-one

Following procedure B, bromide **1** was metallated and then condensed with 1-benzylpiperidin-4-one. Purification of the crude product by flash chromatography (silica, 4:1 CH_2Cl_2/MeOH) gave the alcohol (6.31 g, 69%) as an off-white solid: ^{1}H NMR (300 MHz, CD_3OD): δ 7.40–7.25 (m, 7H), 7.02 (d, $J = 8$ Hz, 1H), 3.62 (s, 2H), 2.80 (d, $J = 11$ Hz, 2H), 2.58 (dt, $J = 12$, 2 Hz, 2H), 2.11 (dt, $J = 13$, 4 Hz, 2H), 1.73 (d, $J = 12$ Hz, 2H); ESI MS m/z 325 $[M+H]^+$. Anal. calcd. for $C_{19}H_{20}N_2O_3 \cdot 0.25H_2O$: C, 69.39; H, 6.28; N, 8.52. Found: C, 69.70; H, 6.17; N, 8.48.

6-(1-Benzyl-3-hydroxypyrrolidin-3-yl)-3*H*-benzoxazol-2-one

Following procedure B, bromide **1** was metallated and then condensed with 1-benzylpyrrolidin-3-one. Purification of the crude product by flash chromatography (silica, 4:1 CH_2Cl_2/MeOH) gave the alcohol (1.80 g, 51%) as a pale brown solid: ^{1}H NMR (300 MHz, CD_3OD): δ 7.40–7.22 (m, 7H), 7.02 (d, $J = 8$ Hz, 1H), 3.77 (br s, 2H), 3.07–2.76 (m, 4H), 2.35–2.25 (m, 1H), 2.19–2.11 (m, 1H); ESI MS m/z 311 $[M+H]^+$. Anal. calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.36; H, 5.95; N, 8.95.

REFERENCES

1. (a) Nikam, S. S.; Meltzer, L. NR2B selective NMDA receptor antagonists. *Curr. Pharm. Des.* **2002**, *8* (10), 845–855. (b) Kornberg, B. E.; Lewthwaite, R. A.; Manning, D.; Nikam,

S. S.; Scott, I. L. Piperidine derivatives as subtype selective *N*-methyl-*D*-aspartate antagonists. U.S. Patent 6,642,256; Nov. 4, 2003; (c) Nikam, S. S.; Scott, I. L.; Sherer, B. A.; Wise, L. D. Bicyclic cyclohexylamines and their use as NMDA receptor antagonists. U.S. Patent 6,794,402; Sept. 21, 2004.

2. Kanyonyo, M. R.; Ucar, H.; Isa, M.; Carato, P.; Lesieur, D.; Renard, P.; Poupaert, J. H. Solvent effect in the Willgerodt–Kindler reaction. *Bull. Soc. Chim. Belg.* **1996**, *105* (1), 17–22.
3. Aichaoui, H.; Lesieur, D.; Hénichart, J.-P. A convenient and efficient method for the preparation of 6-acyl-2(3*H*)-benzoxazolones. *J. Heterocycl. Chem.* **1992**, *29* (1), 171–175.
4. Petrov, O. I.; Kalcheva, V. B.; Antonova, A. T. C-Formylation of some 2(3*H*)-benzazolones and 2*H*-1,4-benzoxazin-3(4*H*)-one. *Collect. Czech. Chem. Commun.* **1997**, *62* (3), 494–497.
5. Ucar, H.; Van derpoorten, K.; Depovere, P.; Lesieur, D.; Isa, M.; Masereel, B.; Delarge, J.; Poupaert, J. H. "Fries-like" rearrangement: A novel and efficient method for the synthesis of 6-acyl-2(3*H*)-benzoxazolones and 6-acyl-2(3*H*)-benzothiazolones. *Tetrahedron* **1998**, *54*, 1763–1772.
6. Taverne, T.; Depreux, P.; Lesieur, D.; Hénichart, J.-P.; Poupaert, J. H. $AlCl_3$-DMF complex as catalyst in the Friedel–Craft reaction: The reactivity of anhydrides and chlorides of dicarboxylic acids. *Bull. Soc. Chim. Belg.* **1997**, *106* (12), 791–801.
7. Gage, J. R.; Perrault, W. R.; Poel, T.-J.; Thomas, R. C. Stereodivergent synthesis of sulfoxide-containing oxazolidinone antibiotics. *Tetrahedron Lett.* **2000**, *41*, 4301–4305.
8. Herrinton, P. M.; Owen, C. E.; Gage, J. R. Iodination and metal halogen exchange of aromatic compounds: An improved preparation of a key oxazolidinone antibiotic intermediate. *Org. Process. Res. Dev.* **2001**, *5* (1), 80–83.
9. Kalcheva, V. B.; Deligeorgiev, T. G.; Zaneva, D. A. An improved method for the halogenation of 2(3*H*)-benzoxazolones. *Dyes Pigments* **1991**, *15*, 275–278.