Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2348–2350
Tetrahedron Letters

Two-step *N*-acylindazole to *N*-alkylindazole reduction. Further synthetic studies on the serotonergic agonist AL-34662

Raymond E. Conrow [a,*], Pete Delgado [a], W. Dennis Dean [a], Gary R. Callen [b], Scott V. Plummer [b]

[a] *Alcon Research, Ltd, Chemical Preparations Research, 6201 South Freeway, R8-6, Fort Worth, TX 76134, United States*
[b] *AMRI Syracuse Research Center, 7001 Performance Drive, North Syracuse, NY 13212, United States*

Received 21 December 2007; revised 6 February 2008; accepted 14 February 2008
Available online 20 February 2008

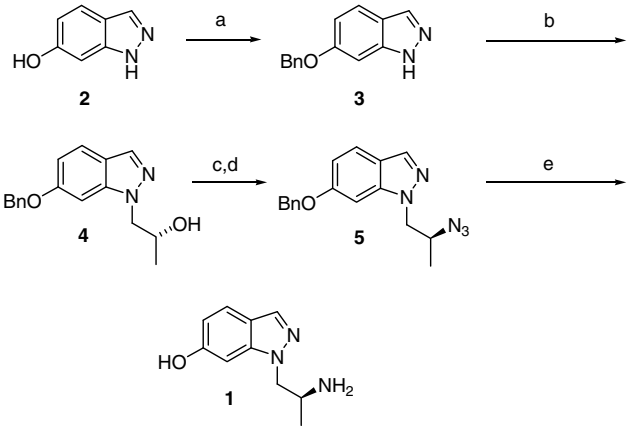
Abstract

A synthesis of the title compound, operable on kilogram scale, employs reductive acetylation of an *N*-acylindazole to give a hemiaminal acetate followed by deacetoxylation to the corresponding *N*-alkylindazole.

Recent publications have described the synthesis, medicinal chemistry, and pharmacology of 1-(*S*)-(2-aminopropyl)-1*H*-indazol-6-ol (**1**, AL-34662), an experimental 5-HT_2 serotonergic receptor agonist under investigation by Alcon for the treatment of elevated intraocular pressure associated with glaucoma.[1] The discovery synthesis of **1** is summarized in Scheme 1.[1a]

To redress issues of regioselectivity encountered in the alkylations leading from indazol-6-ol (**2**) to intermediate **4**, a second-generation synthesis was developed as outlined in Scheme 2.[2,3] Heating fluoro nitrile **6** with (*R*)-1-amino-2-propanol afforded anilino nitrile **7**, which was reduced[4] to aldehyde **8**. Nitrosation of **8** and reduction in situ led to **4**. A variant sequence proceeded via amino indazole **9**. These routes proved useful for preparing **1** in multihundred gram lots.

In this Letter, we disclose key results of further synthetic studies on **1**, highlighted by the reduction of an *N*-acylindazole to the corresponding *N*-alkylindazole via a hemiaminal acetate (Scheme 3, **11**→**12**→**13**). This reduction sequence enabled upstream utilization of an L-alanine-derived sidechain component, thereby avoiding further scaleup of azide chemistry (i.e., **4**→**5**).[5]

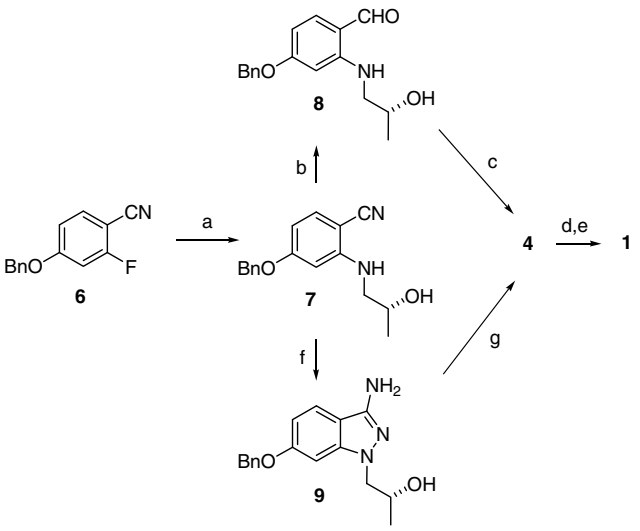


Scheme 1. Discovery synthesis of **1**. Reagents and conditions: (a) BnBr, K_2CO_3, EtOH, 35%; (b) (*R*)-propylene oxide, NaOEt, EtOH, 47%, plus 38% of the *N*2-alkyl isomer; (c) MsCl, Et_3N, CH_2Cl_2; (d) NaN_3, DMF, 70 °C; (e) NH_4OCHO, Pd(C), EtOH, 53% from **4**.

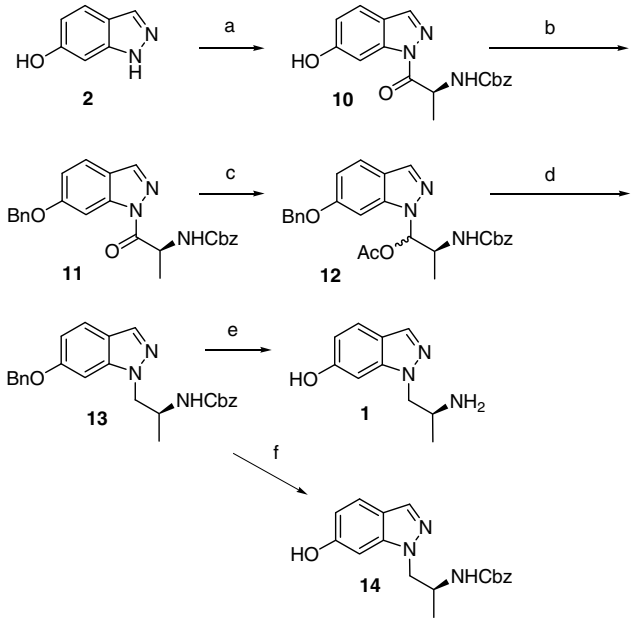
As in the case of **3**→**4**, reaction of **3** with the tosylate of Cbz-L-alaninol[6] or the related bromide followed the usual course of indazole alkylation to give mixtures of the *N*1-alkyl product **13** and its *N*2-alkyl regioisomer. The cyclic sulfamate of Boc-L-alaninol[7] gave comparable results.

* Corresponding author. Tel.: +1 817 551 4542; fax: +1 817 568 7656.
E-mail address: ray.conrow@alconlabs.com (R. E. Conrow).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.086



Scheme 2. Second-generation synthesis of **1**. Reagents and conditions: (a) (*R*)-1-amino-2-propanol, Al_2O_3, DMSO, 125 °C, 81%; (b) NaH_2PO_2, Ni(Ra), Py–HOAc–H_2O, 45 °C, 90%; (c) $NaNO_2$, HOAc–H_2O; Zn, 78%; (d) to give **5**: MsCl, Et_3N, CH_2Cl_2; NaN_3, DMF, 70 °C, 84%; (e) NH_4OCHO, Pd(C), EtOH, 77%; (f) *t*-BuONO, THF; Zn, MeOH, aq NH_4OAc, 78%; (g) *i*-BuONO, MeOH, aq H_3PO_2, 67%.



Scheme 3. Third-generation synthesis of **1**. Cbz = CO_2Bn. Reagents and conditions: (a) Cbz-L-Ala-OSu, K_2CO_3, MeCN; (b) BnBr, K_2CO_3, MeCN, 35 °C, 76% from **2**; (c) Red-Al, toluene, −25 °C; Ac_2O; DMAP, → 23 °C; (d) Et_3SiH, BF_3 etherate, CH_2Cl_2, 60% from **11**; (e) NH_4OCHO, Pd(C), EtOH, THF, 90%; (f) BCl_3, CH_2Cl_2, −45 °C, 79%.

Preparative separation or recycling of the *N*2-alkyl isomer appeared unpromising: *N*2→*N*1 alkyl migration in indazoles has been deployed synthetically, but the scope is limited to cases in which alkylation is readily reversible.[8]

In comparison, *N*2→*N*1 acyl migration is general and facile.[9] Accordingly, we found that reaction of **2** with the succinimidyl ester of Cbz-L-alanine in acetonitrile in the presence of 2 equiv of K_2CO_3 afforded 1-acylindazole **10** to the practical exclusion of the transient 2-acyl isomer. Compound **10** was converted to the benzyl ether **11**, mp 149–151 °C.

With this solution to the regiochemical problem in hand, we turned to the conversion of acylindazole **11** to alkylindazole **13**. It was expected that, due to the low basicity of the indazole anion,[10a] this system would be predisposed to undesired C–N bond cleavage upon metal hydride reduction. Borane–THF has proven effective in overcoming this tendency, of either steric or electronic origin, in amides such as azetidin-2-ones[11] and *N*-acylindoles.[10b,12] Alane has been deployed likewise,[11] with attendant experimental complexities.[13] However, our numerous attempts to reduce **11** to **13** in a one-flask operation using these or other hydrides of B or Al resulted instead in preponderant C–N cleavage to give **3**.

Mindful of Rychnovsky's reductive acetylation–deacetoxylation sequence for converting esters to ethers,[14] we then succeeded at converting **11** to **13** in two steps. Addition of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Red-Al®) to a toluene solution of **11** at -25 ± 5 °C deprotonated and thus protected the NHCbz group. Reduction of the carbonyl group of interest followed. By TLC, the resulting hemiaminal aluminate appeared as its hydrolytic breakdown product **3**.

The cold reaction mixture was quenched with acetic anhydride, DMAP, and pyridine, then warmed to 23 °C to yield hemiaminal acetate **12**. For reactions on <10 mmol scale, a premixed acetylating solution worked well, but on scaleup increasing amounts of **3** appeared at the expense of **12**. A parallel scale effect in an ester reduction was attributed to difficulties with temperature control.[14b] On the surmise that DMAP–pyridine acts in part to promote the dissociation of the key O–Al bond, thereby accelerating both acetylation to **12** and breakdown to the aluminate of **3**, we altered the quenching procedure to maintain an excess of acetylating agent throughout: Ac_2O (6 equiv) was added, then DMAP in pyridine. This proved effective. Further trials established that pyridine could be omitted. Thus, 0.2 equiv of DMAP sufficed to promote >90% conversion of **11** to **12** on 1-mol scale; 85% conversion was realized on 7-mol (3-kg) scale by the use of 1 equiv of DMAP.

In pilot experiments performed with *i*-Bu_2AlH in dichloromethane at −70 °C, **12** was obtained in a 6:1 diastereomeric ratio (dr). Analogous reductions of 2-(NHCbz)-propiophenones have been shown to favor the anti-configured products.[15] The dr of **12** had little influence on the subsequent transformation to **13**. We later came to prefer Red-Al over *i*-Bu_2AlH for ease and safety of handling and workup.[16]

Compound **12** proved stable to routine handling including preparative chromatography on silica, but was typically carried forward without purification. The +APCI mass spectrum of **12** was dominated by an ion of $m/z = 414$, consistent with heterolysis in the desired manner.

Treatment of **12** with Et_3SiH or *n*-$BuMe_2SiH$[17,18] and BF_3 etherate (2 equiv of each) in CH_2Cl_2 at 23 °C then gave **13**, mp 119.5–122.5 °C, in 60% yield from **11** after crystallization from *n*-BuCl–hexane. The enantiomeric excess of such material was determined to be 97%, corresponding to that of the L-Ala component used to prepare **10**. Notably, acylindazole **11** proved inert to reduction under these conditions.

General precedent for this deacetoxylation step can be discerned in a report by Mayr of the conversion of *N*-(1-acetoxyethyl)carbazole to *N*-ethylcarbazole by treatment with Et_3SiH and TMSOTf.[19] The former substance was obtained by the addition of carbazole[10c] to vinyl acetate,[20] a method that in several variants has yielded other simple racemic azole adducts.[21] Silane deoxygenation of hemiaminal structures is more typically practiced in the nonaromatic domain, exemplified by 2-hydroxy- and 2-acyloxypyrrolidines and the corresponding piperidines.[22]

The synthesis of **1** was completed by hydrogenolysis of **13**. Alternatively, exposure of **13** to 3.5 mol equiv of boron trichloride in CH_2Cl_2 at −45 °C selectively cleaved the aryl benzyl ether to provide the monoprotected derivative **14**.

In summary, the new route shown in Scheme 3 redresses prior issues related to alkylation regiochemistry and amino group emplacement, without recourse to chromatography and with no increase in step count from Scheme 1 common intermediate **2**. The scope and scale of hemiaminal ester formation and deoxygenation have been enlarged to encompass an indazole-derived substrate bearing an adjacent stereocenter. Refinements and scaleup studies are ongoing and will be reported in due course.

References and notes

1. (a) May, J. A.; Dantanarayana, A.; Zinke, P. W.; McLaughlin, M. A.; Sharif, N. A. *J. Med. Chem.* **2006**, *49*, 318; (b) Sharif, N. A.; McLaughlin, M. A.; Kelly, C. R. *J. Ocul. Pharmacol. Ther.* **2007**, *23*, 1.
2. (a) For details see the examples and relevant discussion in: Conrow, R. E.; Delgado, P.; Dean, W. D.; Pierce, D. R.; Gaines, M. S. U.S. Patent 6,998,489B1; (b) Delgado, P.; Conrow, R. E.; Dean, W. D. PCT WO2004/058725A1.
3. Ref. 2a also details the synthesis of (±)-**8** from 6-benzyloxyindole by the sequence: propylene oxide/NaH, O_3/Me_2S, NaOH.
4. East, S. P.; Joullié, M. M. *Tetrahedron Lett.* **1998**, *39*, 7211.
5. Caution: This common method for converting alcohols to azides carries the risk of diazidomethane formation, to be discussed in a future publication.
6. Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083.
7. Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164.
8. For example, see: (a) Saenz, J.; Mitchell, M.; Bahmanyar, S.; Stankovic, N.; Perry, M.; Craig-Woods, B.; Kline, B.; Yu, S.; Albizati, K. *Org. Process Res. Dev.* **2007**, *11*, 30; (b) Batt, D. G.; Petraitis, J. J.; Houghton, G. C.; Modi, D. P.; Cain, G. A.; Corjay, M. H.; Mousa, S. A.; Bouchard, P. J.; Fortsythe, M. S.; Harlow, P. P.; Barbera, F. A.; Spitz, S. M.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 41; (c) Seela, F.; Peng, X. *Nucleosides, Nucleotides Nucleic Acids* **2004**, *23*, 227; (d) López, M. C.; Claramunt, R. M.; Ballesteros, P. *J. Org. Chem.* **1992**, *57*, 5240.
9. Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. M., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 167–303. cf. pp 212, 232.
10. (a) The pK_a of indazole in DMSO is estimated to be 17.7 by interpolation from pK_a values of azoles and their benzo derivatives in Ref. 10d; (b) pK_a of indole = 20.95;[10d] (c) pK_a of carbazole = 19.9;[10d] (d) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. www.chem.wisc.edu/areas/reich/pkatable/.
11. Jackson, M. B.; Mander, L. N.; Spotswood, T. M. *Aust. J. Chem.* **1983**, *36*, 779.
12. (a) Biswas, K. M.; Dhara, R.; Roy, S.; Mallik, H. *Tetrahedron* **1984**, *40*, 4351; (b) Biswas, K. M.; Dhara, R. N.; Mallik, H.; Halder, S.; Sinha-Chaudhuri, A.; De, P.; Brahmachari, A. S. *Indian J. Chem.* **1991**, *30B*, 906.
13. Carey, D. T.; Mair, F. S.; Pritchard, R. G.; Warren, J. E.; Woods, R. J. *Dalton Trans.* **2003**, 3792.
14. (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191; (b) Kopecky, D. J.; Rychnovsky, S. D. In *Organic Syntheses*; Wiley: Hoboken, N.J., 2003; Vol. 80, pp 177–183.
15. Yin, J.; Huffman, M. A.; Conrad, K. M.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 840.
16. For a discussion of the workup of *i*-Bu_2AlH reductions on large scale, see: Perrault, W. R.; Shephard, K. P.; LaPean, L. A.; Krook, M. A.; Dobrowolski, P. J.; Lyster, M. A.; McMillan, M. W.; Knoechel, D. J.; Evenson, G. N.; Watt, W.; Pearlman, B. A. *Org. Process Res. Dev.* **1997**, *1*, 106.
17. *n*-$BuMe_2SiH$ is prepared more economically than Et_3SiH on commercial scale, that is, *n*-BuMgX + $ClSiMe_2H$ versus 3EtMgX + Cl_3SiH: G. L. Larson, Gelest Inc., personal communication.
18. For acetal reduction with various silanes, see: Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266.
19. Schimmel, H.; Ofial, A. R.; Mayr, H. *Macromolecules* **2002**, *35*, 5454.
20. Kricka, L. J.; Ledwith, A. *J. Org. Chem.* **1973**, *38*, 2240.
21. (a) Smith, K.; Hammond, M. E. W.; James, D. M.; Ellison, I. J.; Hutchings, M. G. *Chem. Lett.* **1990**, 351; (b) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683; (c) Xu, J.-M.; Liu, B.-K.; Wu, W.-B.; Qian, C.; Wu, Q.; Lin, X.-F. *J. Org. Chem.* **2006**, *71*, 3991.
22. (a) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053; (b) Hwang, D. J.; Kim, S. N.; Choi, J. H.; Lee, Y. S. *Bioorg. Med. Chem.* **2001**, *9*, 1429; (c) Furukubo, S.; Moriyama, N.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2004**, *45*, 8177; (d) Larson, G. L.; Fry, J. L. In *Organic Reactions*; Wiley: Hoboken, N.J., 2008; Vol. 71, pp 1–735.