Tetrahedron Letters 49 (2008) 6749–6751

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An expedient synthesis of 3-substituted indoles via reductive alkylation with ketones

John R. Rizzo, Charles A. Alt, Tony Y. Zhang *

Chemical Product Research and Development, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, United States

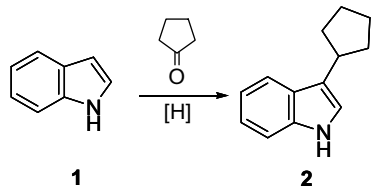
ARTICLE INFO

Article history:
Received 6 May 2008
Revised 2 August 2008
Accepted 8 August 2008
Available online 14 August 2008

ABSTRACT

3-Alkylindoles were prepared in one step from indoles and ketones via a convenient reductive alkylation procedure using triethylsilane and trichloroacetic acid. Under this particular condition, unsubstituted indoles could be tolerated to afford good yields of 3-*sec*-alkylation products.

Indole (**1**) and derivatives with an alkyl substituent at the 3-position are venerable pharmacophores for medicinal chemists, especially in the neuroscience arena, as exemplified by launches of a series of molecules with 5-HT1B/1D receptor agonist activities for the treatment of migraine.[1–3] In support of an ongoing indole research program, we encountered a need for an efficient way to supply a number of 3-alkylated indole derivatives. In particular, 3-cyclopentylindole (**2**) was needed in kilogram quantities to fund preclinical development needs. This led us to a survey of the literature for a direct and versatile method that would address not only the medicinal chemistry requirement for exploring molecular diversity, but also the downstream development need for a scalable synthesis.



1 **2** (1)

Traditional methods of C-3 derivatization center around direct alkylation of unsubstituted indole (**1**) with electrophilic alkyl derivatives, such as alkyl halides, under basic conditions.[4–7] However, these methods suffer from low efficiency and lack of regioselectivity (C-3 vs N-1), especially when the electrophile is sterically hindered such as a secondary alkyl halide. The reaction scope of condensing an indole anion with aldehyde or ketone has been widely used to prepare 3-alkenyl-substituted indoles[6] (**6**, Fig. 1), though reaction scope is limited to a selected group of carbonyl compounds capable of rapidly eliminating a proton to form the alkene under basic conditions. In the event a 3-alkylindole is desired, an extra step of reduction has to be performed. Condensation of indole with ketone or aldehyde under acidic conditions invariably gave rise to bisindolylmethane derivatives (**7**).[7] A recent patent disclosure from a Wyeth group relates reductive alkylation at the 3-position using aldehydes.[8] However, an N-protecting group had to be installed. A reductive alkylation procedure using

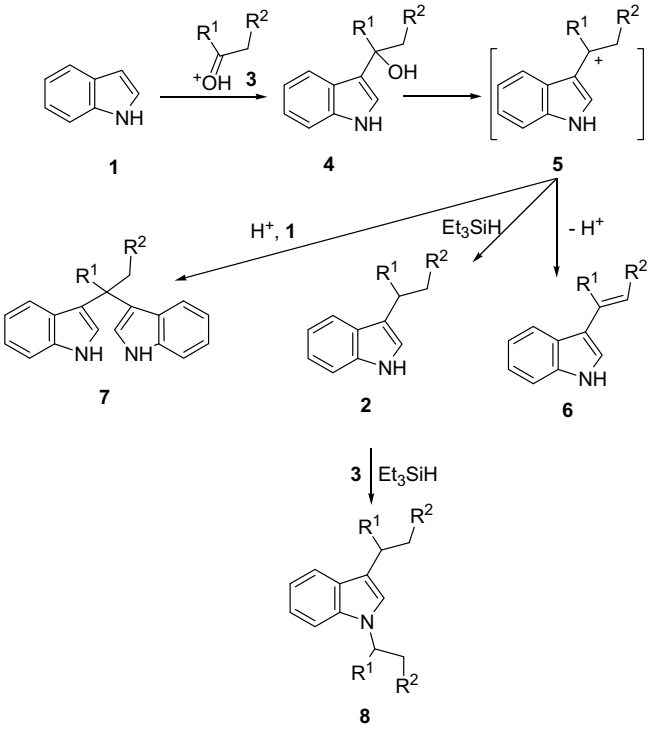


Figure 1.

* Corresponding author. Tel.: +1 317 276 3882; fax: +1 317 276 4507.
E-mail address: Zhang@lilly.com (T. Y. Zhang).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.08.034

Et_3SiH and CF_3CO_2H in dichloromethane at low temperatures, developed by Steele[9] and Mahadevan,[10] thus became attractive to us for several reasons. First, it avoids the use of alkyl halides, a class of compounds oftens associated with mutagenic properties, and hence requires vigorous control in scale-up settings. Secondly, the method appears to be reasonably efficient, affording 3-alkylindole in one simple step. Indeed, the procedure worked well as advertized, affording 3-alkylated indoles in moderate to good yield when aldehydes were used as the alkyl donors. However, yields were low when ketones had to be used in place of aldehydes. The authors[11] also noted that unsubstituted indole failed to afford any identifiable products. In our hands, we were able to isolate, after a prolonged reaction time, 3,1(*N*)-biscyclopentylindole (**8**, R^1–R^2 = –$(CH_2)_3$–) in 38% yield from indole (**1**) and cyclopentanone under the Et_3SiH/CF_3CO_2H conditions. Nonetheless, we were encouraged by the fact that the desired monoalkylated product compound **2** was also isolated in 30% yield from the same reaction mixture.

It appeared to us that the shortcomings associated with 2-unsubstituted indoles in this reductive alkylation reaction are likely a manifestation of increased reactivity of the product **2** toward further reaction with electrophiles. This is likely due to a lack of steric hindrance at the 2-position and higher electron density when an alkyl group is introduced at the 3-position. One way to address the problem is to control the reactive concentration of the electrophiles via slow addition of the ketone to the reaction mixture. However, doing so led to an increased amount of bisindolylmethane (**7**) formation. We reasoned that modulating the reactivities of the oxonium (**3**) and the indolium (**5**) intermediates might provide a solution toward selective formation of **2**, which as an unsubstituted indole is not stable under the strong acidic and reductive conditions.[7] A quick screen of common acids, both Lewis and Brønsted, was conducted using the very demanding substrate, that is, unsubstituted indole (**1**) and cyclopentanone, as a model reaction (Eq. 1). Not surprisingly, stronger acids, such as CF_3SO_3H and sulfuric acid, uniformly led to decomposition of the indole substrate, as did strong Lewis acids such as $ZnCl_2$ and BF_3. Weak acids ($PhCO_2H$, CH_3CO_2H) led to recovery of the starting materials. A balance was found with CCl_3CO_2H, which afforded an acceptable reaction rate for the reductive alkylation, and resulted in minimal product decomposition. However, formation of a substantial amount of bisalkylated product (**8**) persisted. This problem was successfully addressed by a controlled addition of a premixed solution of ketone or aldehyde with indole to a *heated* solution of CCl_3CO_2H. We were also successful at replacing the chlorinated reaction solvents (CH_2Cl_2 or $ClCH_2CH_2Cl$) with environmentally friendlier hydrocarbons (toluene). For example, addition of cyclopentanone and indole to a heated (70 °C) solution of trichloroacetic acid and triethylsilane in toluene provided the desired 3-cyclopentylindole in 65% isolated yield.[11] The improved conditions show very little formation of the biscyclopentylindole (**8**) or the bisindoylmethane (7). Triethylsilane proved to be the best hydride donor, as bulkier silanes such as *i*-Pr_3SiH, *n*-Bu_3SiH, and Ph_2SiH_2 afforded very little product. Other metal hydrides such as *n*-Bu_3SnH hydride or *n*-Bu_3GeH were ineffective.

A reaction scope was briefly investigated (Fig. 2).[12] Both aliphatic and aromatic ketones worked well, except highly hindered substrates such as benzophenone (22%) or unstable ones like 4-tetrahydropyranone (46%). Substituted indoles, including 2-alkylated substrates, also gave good yields. However, 4-bromo and 4-nitroindole failed to react, probably due to a combination of steric hindrance and electron deficiency.

In summary, we were able to demonstrate that reductive alkylation of unsubstituted indoles with ketones can be achieved using trichloroacetic acid and triethylsilane. The procedure has been demonstrated at the kilogram scale, and proved to be robust and convenient. It provides a useful alternative to the existing methods of making substituted indoles, and proved to be a preferred one for introducing *sec*-alkyls into the 3-position without the need for N-protection. Seasoned medicinal chemists would find these compounds convenient building blocks for exploring the pharmacological effect of structural diversity.

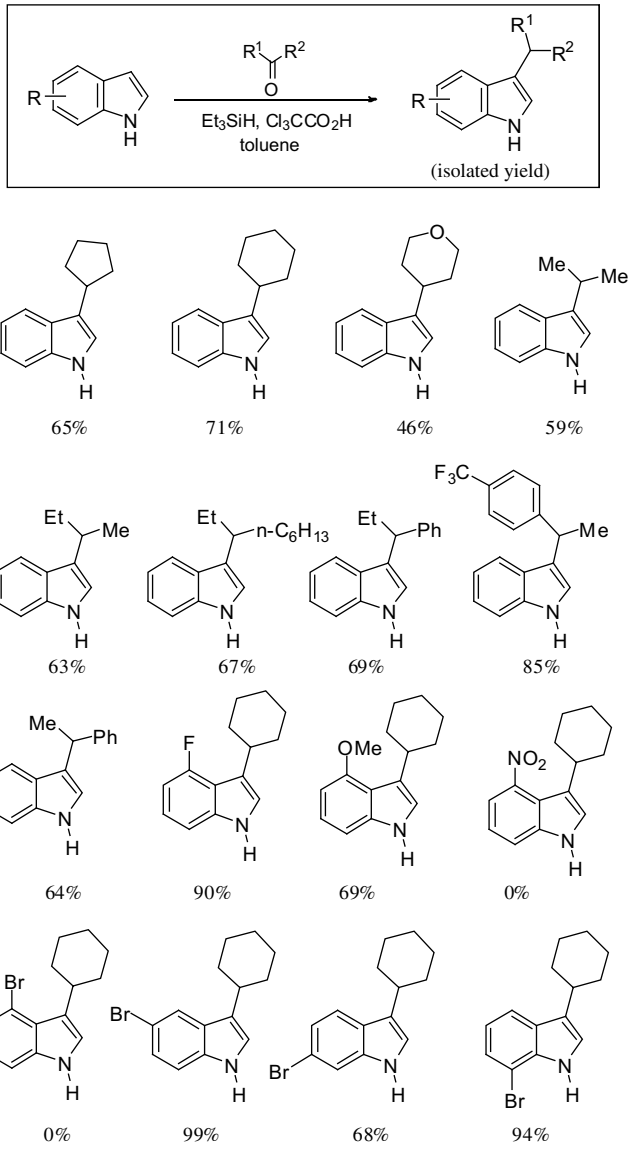


Figure 2. Reductive alkylation of indoles with ketones.

Acknowledgment

The authors wish to thank Dr. Alfio Borghese for demonstrating this chemistry at multi-kilogram scale.

References and notes

1. Buchanan, T. M.; Ramadan, N. M.; Aurora, S. *Exp. Rev. Neurotherap.* **2004**, *4*, 391–402.
2. Goadsby, P. J. *Nat. Rev. Drug Disc.* **2005**, *4*, 741–750.
3. Mannix, L. K.; Files, J. A. *CNS Drugs* **2005**, *19*, 951–972.
4. Attaur, R.; Basha, A. Indole Alkaloids. 1997, p 336.
5. Sundberg, R. J. *Indoles*; Academic Press: New York, 1996.
6. *Indoles: The Monoterpenoid Indole Alkaloids*, Saxton, J. E., Ed.; The Chemistry of Heterocyclic Compounds; 1983; Vol. 25, Pt. 4, p 886.
7. Leete, E. *J. Am. Chem. Soc.* **1959**, *81*, 6023–6026.

8. Michalak, R. S.; Raveendranath, P. PCT Int. Appl., 2005, WO 2005058820, CA 143:97260.
9. Appleton, J. E.; Dack, K. N.; Green, A. D.; Steele, J. *Tetrahedron Lett.* **1993**, *34*, 1529–1532.
10. Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. *Tetrahedron Lett.* **2003**, *44*, 4589–4591.
11. A representative procedure is as follows: A 100 mL flask was charged with triethylsilane (3.49 g, 30 mmol), trichloroacetic acid (2.45 g, 15 mmol), and toluene (5 mL). The solution was heated to 70 °C, and a solution of indole (1.17 g, 10 mmol) and cyclopentanone (0.924 g, 11 mmol) in toluene (5 mL) was added dropwise. The resulting solution was heated at 70 °C for 20 min to drive reaction to completion as judged by GC. The solution was cooled to 10 °C and quenched with saturated aqueous sodium bicarbonate (15 mL) and methyl *tert*-butyl ether (15 mL). The organic layer was separated, dried, and concentrated under vacuum. The crude oil was purified using the CombiFlash system (eluting with hexanes) to give 1.20 g (64.5%) of an oil, which crystallizes upon standing: ^{1}H NMR (300 MHz, $CDCl_3$) 7.9 (1H, br s), 7.7 (1H, d), 7.4 (1H), 7.3 (1H, m), 7.2 (1H, m), 7.0 (1H, s), 3.3 (1H, m), 2.2 (2H, m), 1.9 (1H, m), 1.8 (3H, m), 1.0 (1H, m), 1.6 (1H, m); HRMS theory 185.1204, found 185.1212.
12. All products were isolated and characterized using NMR, IR, and HRMS.