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Regiocontrolled Synthesis of Carbocycle-Fused Indoles via Arylation of Silyl Enol Ethers with *o*-Nitrophenylphenyliodonium Fluoride

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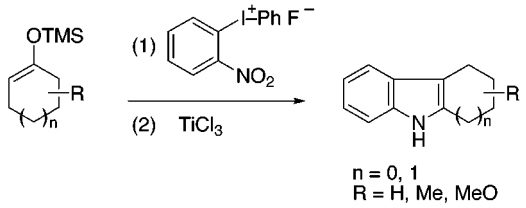
ABSTRACT



A new, regiocontrolled synthesis of carbocycle-fused indoles has been developed. The two-step procedure involves first the regiospecific arylation of silyl enol ethers with *o*-nitrophenylphenyliodonium fluoride (1). Reduction of the nitro group on the aromatic ring with $TiCl_3$ followed by spontaneous condensation of the aniline with the ketone then affords the indole products.

Indoles are among the most prevalent heterocycles. The indole nucleus is found in numerous natural products and constitutes the integral part of several families of alkaloids, many with significant pharmacological activities.[1] Consequently, considerable effort has been directed toward developing new methods for the construction of the indole unit.[2] One of the oldest and yet most widely used methods for preparing indoles is the Fischer indole synthesis.[3] A limitation of this method, however, is the lack of regioselectivity with unsymmetrical ketones having two enolizable sites. The Fischer method produces the indole that arises from the thermodynamically more stable enehydrazine. The regioselective[4] synthesis of indoles from such ketones remains an important and actively pursued problem. In connection with our interest in the stereoselective synthesis of *Aspidosperma* alkaloids,[5] we have explored methods for the regiocontrolled synthesis of the indole sector of tabersonine and have developed a new, two-step synthesis of carbocycle-fused indoles.

Our method is based on the direct, regiospecific *o*-nitrophenylation of an enol silyl ether (Scheme 1).[5−7] Subsequent reduction of the nitro group on aryl ketone **3** followed by spontaneous cyclization affords the indole

(1) Recent reviews: (a) Herbert, R. B. *The Monoterpenoid Indole Alkaloids*, supplement to vol. 25, part 4 of *The Chemistry of Heterocyclic Compounds*; Saxton J. E., Ed.; Wiley: Chichester, 1994. (b) Saxton, J. E. *Nat. Prod. Rep.* **1997**, 559−590. (c) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, Chapter 9. (d) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1. (e) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, 327−340, and references therein.

(2) (a) Gribble, G. W. *Contemp. Org. Chem.* **1994**, *1*, 145−172. (b) Sundberg, R. J. *Indoles*; Academic Press: San Diego, CA, 1996. (c) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 2, pp 119−206. (d) Döpp, H.; Döpp, D.; Langer, U.; Gerding, B. In *Methoden der Organischen Chemie*; Kreher, R., Ed.; Georg Thieme Verlag: Stuttgart, 1994; Hetarene I, Teil 2, pp 546−1336, and references therein.

(3) (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607−632.

(4) (a) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468−4475. (b) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791−3792, and references therein.

(5) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523−13524.

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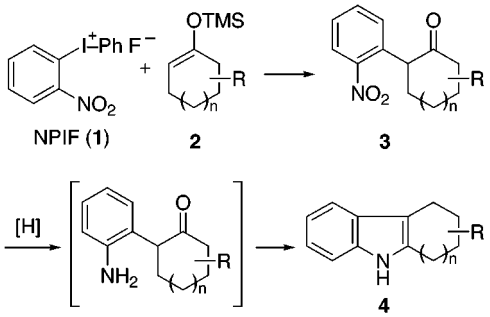
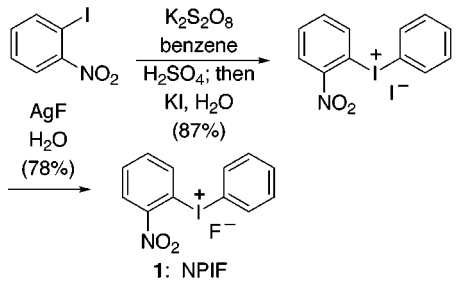
Scheme 1



products. The regiospecificity of this indole synthesis stems from the starting silyl enol ethers, which can be easily prepared in a highly or completely regiocontrolled manner by, *inter alia*, (a) kinetic[8] or thermodynamic[9] enolization of ketones, (b) Li/NH_3 reduction of enones,[10] and (c) 1,4-addition of cuprates to enones.[11]

The required arylating reagent, *o*-nitrophenylphenyliodonium fluoride (NPIF, **1**),[12] was conveniently prepared in two steps (Scheme 2). The reaction of *o*-iodonitrobenzene with

Scheme 2



benzene under oxidizing conditions followed by treatment with aqueous KI gave *o*-nitrophenylphenyliodonium iodide as an orange solid.[13] The exchange of iodide counterion with fluoride gave the desired nitrophenylating reagent.

On the basis of the work of Beringer et al.,[13b] the more electron deficient *o*-nitrophenyl group was expected to transfer during the arylation. The reaction conditions for the *o*-nitrophenylation were optimized using the TMS ether of cyclohexanone (Table 1, entry 1).[14] A stirred solution of NPIF (**1**) (345 mg, 1 mmol) in dry DMSO−CH_2Cl_2 (1.4−2.1 mL) was treated dropwise with neat TMS ether **2** (1 mmol) at ca. −40 °C (CO_2−MeCN). The mixture was stirred at this temperature for 2 h and then allowed to warm to room temperature gradually over 2−3 h. Standard extractive workup and chromatographic purification yielded the arylated ketone **3** in 89% yield (Table 1). As expected,[13] no 2-phenylcyclohexanone had formed. The use of a polar solvent was critical for successful arylation. The yield of the arylated product was considerably lower (53%) when using the *tert*-butyldimethylsilyl (TBS) enol ether **2a′** instead of the TMS ether (entry 2).[15] The example in entry 3 illustrates the regiocontrol possible using the present methodology. Treatment of enol silyl ether **2b**, obtained from the kinetic enolate of 2-methylcyclohexanone,[8] with NPIF gave **3b** in good yield.[16] The regiocontrol capability of the nitrophenylation was further tested through the reaction of substrate **2c**, prepared by the reaction of 2-cyclohexenone with dimethylcuprate followed by TMSCl.[11a] Despite the greater steric crowding at the adjacent carbon, arylation of **2c** gave the desired ketone in good yield as essentially a single diastereomer (entry 4). Arylation of the methoxy-substituted silyl ether **2e**[17] provided cyclohexanone **3e** in 75% yield (entry 6).

(6) Preparation of indoles via direct arylation of ketone enolates or their equivalents has been previously investigated. For example, see: (a) Kuehne, M. E. *J. Am. Chem. Soc.* **1962**, *84*, 837−847. (b) Gassman, P. G.; Van Bergen, T. J. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 6, pp 50−59. (c) RajanBabu, T. V.; Reddy, G. S.; Fukunaga, T. *J. Am. Chem. Sco.* **1985**, *107*, 5473−5483. (d) RajanBabu, T. V.; Chenard, B. L.; Petti, M. A. *J. Org. Chem.* **1986**, *51*, 1704−1712.

(7) Phenylation of TMS enol ethers using diphenyl iodonium fluoride has been reported: Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764−5767.

(8) (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. G. *J. Org. Chem.* **1969**, *34*, 2324−2336. (b) Lessene, G.; Tripoli, R.; Cazeau, P.; Brian, C.; Bordeau, M. *Tetrahedron Lett.* **1999**, *40*, 4037−4040.

(9) (a) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345−1348. (b) Orban, J.; Turner, J. V.; Twitchin, B. *Tetrahedron Lett.* **1984**, *25*, 5099−5102.

(10) (a) Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181−6182. (b) Brown, P. A.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1303−1309.

(11) (a) Binkley, E. S.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2156−2160. (b) Dieter, R. K.; Dieter, J. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1378−1380.

(12) **Preparation of NPIF (1). (a) *o*-Nitrophenylphenyliodonium Iodide.** To a stirred solution of *o*-iodonitrobenzene (5.0 g, 20 mmol) in H_2SO_4 (100 mL) was added $K_2S_2O_8$ (6.0 g, 22 mmol) in small portions followed by benzene (25 mL) at room temperature, and the mixture was stirred vigorously for 1.5 h. The reaction mixture was poured into ice (total volume 300 mL), and the insoluble material was removed by filtration. The filtrate was treated with aqueous KI (5 g/20 mL of H_2O), giving an orange precipitate that was filtered and washed thoroughly with H_2O (250 mL) followed by a small amount of acetone. The collected solid was dried over P_2O_5 under reduced pressure to give 7.95 g (87%) of the iodonium iodide. This procedure was developed from the method of Beringer et al. (ref 13a, note the typographical error in their original procedure: *o*-iodosonitrobenzene should be replaced with *o*-iodonitrobenzene). **(b) *o*-Nitrophenylphenyliodonium Fluoride**. To a vigorously stirred solution of AgF (1.0 g, 7.9 mmol) in H_2O (30 mL) was added the iodonium iodide (3.6 g, 7.9 mmol), and the mixture was stirred for several hours. After removal of the insoluble material by filtration, the solution was concentrated below 30 °C under reduced pressure (<5 Torr). The residue was diluted with 8 mL of MeCN and crystallized at 0 °C to give NPIF (**1**, 1.80 g first crop, 0.33 g second crop; total 2.13 g, 78%).

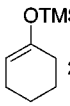
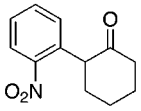
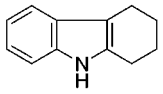
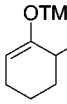
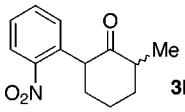
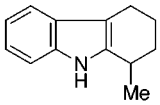
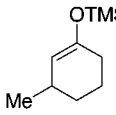
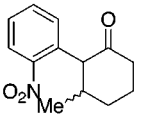
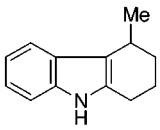
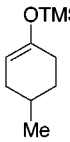
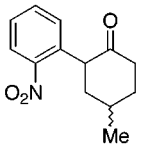
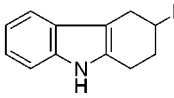
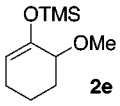
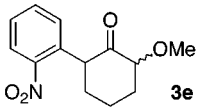
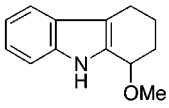
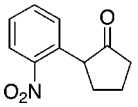
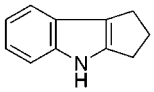
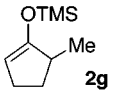
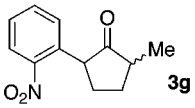
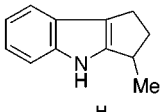
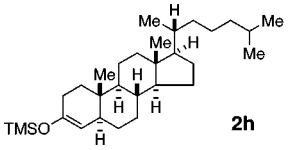
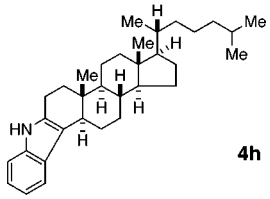
(13) (a) Beringer, F. M.; Gindler, E. M.; Rapoport, M.; Taylor, R. J. *J. Am. Chem. Soc.* **1959**, *81*, 351−361. (b) Beringer, F. M.; Forgione, P. S.; Yudis, M. D. *Tetrahedron* **1960**, *8*, 49−63.

(14) **General Procedure for Arylation Reaction.** To a stirred solution of NPIF (**1**) (345 mg, 1 mmol) in dry DMSO−CH_2Cl_2 (1.4−2.1 mL) was added TMS ether **2** (1 mmol) dropwise at ca. −40 °C (CO_2−MeCN) under nitrogen. The mixture was stirred for 2 h at this temperature and allowed to warm to room temperature gradually over 2−3 h. The reaction mixture was poured into H_2O (10 mL), and the whole was extracted with ether (10 mL × 3). The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc:hexanes = 1:30−1:5) to give the aryl ketone (**3**). Aryl ketones **3** were characterized from ^1H and ^{13}C NMR and IR spectra. See Supporting Information for the spectral data as well as copies of actual spectra.

(15) The modest yield for this example stands in contrast with the high yield obtained for the *o*-nitrophenylation of a complex intermediate leading to the natural product tabersonine (ref 5).

(16) Product **3b** was obtained as an inseparable 12:1 mixture (by ^1H NMR) of cis−trans isomers.

Table 1. Regiocontrolled Synthesis of Indoles *via* Arylation of Silyl Enol Ether Followed by $TiCl_3$ Reduction

Entry	Silyl Enol Ether	Aryl Ketone	Yield (%)[a]	Indole	Yield (%)[a]
1	 **2a**	 **3a**	89	 **4a**	88
2	**2a'**=TBS ether		53		
3	 **2b**	 **3b**	75[b]	 **4b**	78
4	 **2c**	 **3c**	78[c]	 **4c**	89
5	 **2d**	 **3d**	87[d]	 **4d**	89
6	 **2e**	 **3e**	75[e]	 **4e**	60[i]
7	 **2f**	 **3f**	47 (56)[f]	 **4f**	86
8	 **2g**	 **3g**	46[f,g]	 **4g**	71
9	 **2h**		–[h]	 **4h**	18[j]

[a] Isolated yield. [b] An inseparable mixture of stereoisomers (*ca.* 1:12 by ^{1}H NMR). [c] Essentially one isomer (> 95%). [d] An inseparable mixture of stereoisomers (*ca.* 1:4.8 by ^{1}H NMR). [e] Stereoisomers separated on TLC, but interconverted during silica gel column chromatography. [f] HMPA-THF (1:1) used as solvent. [g] An inseparable mixture of stereoisomers (*ca.* 1:4.4 by ^{1}H NMR). [h] Aryl ketone was not isolated. The crude ketone was used in $TiCl_3$ reduction after removal of less-polar materials (e.g., iodobenzene and nitrobenzene) by silica gel column chromatography. [i] $TiCl_3$ solution was added to a buffered solution of the aryl ketone. [j] Overall yield (2 steps) from TMS ether.

In comparison with the examples discussed above, the TMS ethers of cyclopentanone and its derivatives were less effective as substrates for the arylation reaction. The reaction of **2f** with NPIF in 1:1 DMSO−CH_2Cl_2 gave the arylated cyclopentanone **3f** in only moderate yield. The yield of **3f** improved to 56% by carrying out the reaction in 1:1 HMPA−THF (entry 7, in parentheses). The methylcyclopentanone derivative **3g** was formed in 46% yield as an inseparable mixture of cis:trans diastereomers (entry 8). Enol TMS ethers of acyclic ketones, camphor, and cyclohexenone (kinetic enolate) were poor substrates for this arylation reaction. Nitrobenzene was the main byproduct in all arylation reactions. A small amount of the enone corresponding to the enol ether was also observed in the product mixture, arising presumably from disproportionation competing with radical coupling.[7]

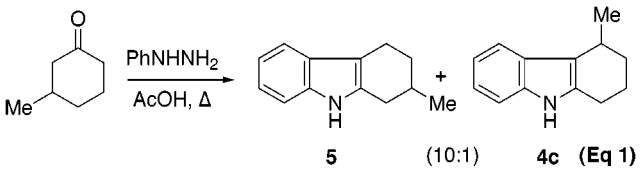
The *o*-nitrophenyl-substituted ketones (**3**) were efficiently converted into the corresponding indoles upon reduction with $TiCl_3$,[18] a reagent that appears to be underutilized for the reduction of nitro groups (Table 1). This reduction was readily carried out by dropwise addition of a solution of the nitrophenyl ketone (**3**) in acetone at room temperature to a

(17) Ghiron, C.; Piga, E.; Rossi, T.; Tamburini, B.; Thomas, R. J. *Tetrahedron Lett.* **1996**, *37*, 3891−3894.

(18) (a) Ho, T.-L.; Wong, C. M. *Synthesis* **1974**, 45. (b) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 673−679.

vigorously stirred two-phase mixture containing aqueous $TiCl_3$, aqueous NH_4OAc, and acetone.[19] The reactions proceeded smoothly, typically going to completion in just 15 min, and afforded the indole products (**4**) in good to high yields. In the case of methoxy derivative **4e**, an aqueous solution of $TiCl_3$ was added to a two-phase ammonium acetate buffer solution of aryl ketone **3e** in H_2O−acetone in order to avoid decomposition of the labile product (entry 6). We also utilized the arylation−reductive indolization sequence for the regoicontrolled synthesis of a cholestene-fused indole (entry 9). The steroidal enol silyl ether **2h**, prepared regioselectively from 4-cholesten-3-one by the Birch reduction−silylation sequence,[10] was treated with NPIF to afford the arylated ketone. Direct reduction of the crude ketone using $TiCl_3$ gave indole **4h** as the sole regioisomer, albeit in low yield.

The present method has allowed the synthesis of indoles that would be difficult to obtain by conventional means. For example, the Fischer indole synthesis using 3-methylcyclohexanone is reported to afford a mixture of regioisomers, with tetrahydrocarbazole **5** being formed in preference to **4c** (eq 1).[20] The recently developed palladium-catalyzed annulation between 2-iodoaniline and 3-methylcyclohexanone is also reported to give **5** as the major product.[21] By contrast, using the present method, indole **4c** can be obtained as the sole regioisomer. Also worthy of note is the exclusive formation of cholestene-fused indole **4h**, a regioisomer that is reportedly not formed from cholestan-3-one using the palladium-catalyzed method.[21]



5 (10:1) **4c** **(Eq 1)**

In summary, we have developed a new method for the regiocontrolled synthesis of carbocycle-fused indoles. It is a two-step procedure involving *o*-nitrophenylation of silyl enol ethers using NPIF followed by reduction of the nitro group with $TiCl_3$, which yields the indole products.

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Supporting Information Available: ^1H NMR and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) **General Procedure for $TiCl_3$ Reduction.** Aqueous $TiCl_3$ can be purchased from Aldrich. Alternatively, it can be prepared inexpensively by dissolving $TiCl_3 \cdot {}^1/_3AlCl_3$ (available from Strem Chemicals, Inc.) in water (CAUTION! Strong exotherm!) and filtering off the precipitate. The concentration of the purple solution can be determined by titrating with 0.1 M $KBrO_3$, wherein disappearance of the purple color indicates the endpoint. To a purple solution of 1.44 M $TiCl_3$ in H_2O (0.56 mL, 0.8 mmol of $TiCl_3$) was added 2.5 M NH_4OAc in H_2O (1 mL) followed by acetone (1 mL) at room temperature. The purple color turned dark brown, and the mixture formed a two-phase system. A solution of a nitro ketone **3** (0.1 mmol) in acetone (1 mL) was added dropwise at room temperature with vigorous stirring. After 15 min, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL × 3). The extracts were washed with a $NaHCO_3$ aqueous solution followed by brine and then dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc:hexanes = 1:60−1:50, containing a small amount of Et_3N) to give the indole product (**4**).

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