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One-pot synthesis of *N*-substituted 2-methyl-4,5,6,7-tetrahydroindole derivatives

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Abstract—We describe the preliminary results of one-pot syntheses of various *N*-substituted 2-methyl-4,5,6,7-tetrahydroindole derivatives from 2-(2-bromoallyl)cyclohexanone and the corresponding primary amines in good yields. Aliphatic amines were directly converted to tetrahydroindoles, whereas aromatic amines needed an extra base treatment step to complete the transformation.

1. Introduction

The biological activity of some pyrrole derivatives has prompted the development of new synthetic pathways for 4,5,6,7-tetrahydroindoles with various substitution patterns.[1a–m] Different tetrahydroindoles are found in the structures of many biologically active compounds, such as antibiotics,[2] antipsychotic agents[3] and blood-platelet aggregation inhibitors.[4a,b] They can also be used as ligands for transition metals.[5] Various multistep synthetic procedures have been described in the literature, including reduction of indoles[6a–c] or annulation reactions.[1e] Although there are several methods for the synthesis of 4-oxo-4,5,6,7-tetrahydroindoles from 1,3-dicarbonyl compounds,[7a,b] the synthesis of tetrahydroindoles without a carbonyl group in the cyclohexane ring requires multistep procedures.[8] The factors outlined above directed our efforts towards the development of a one-pot procedure for the synthesis of various *N*-substituted 2-methyl-4,5,6,7-tetrahydroindoles. Here we report the results obtained from our work.

2. Results and discussion

2-(2-Bromoallyl)cyclohexanone **1** was chosen as starting compound and was prepared according to slightly modified literature procedures.[7b,9] 1-Pyrrolidino-1-cyclohexene (1 equiv) was reacted with 2,3-dibromopropene (1.2 equiv) in dry dioxane, with the addition of 1 equiv of triethylamine and the mixture was refluxed for 6 h. The resultant mixture was subsequently refluxed with 1 N HCl for an additional 3 h to afford **1** with an improved yield of 65%. Mixing **1** with 1.5 equiv of various primary amines and a drying agent ($MgSO_4$) in dry toluene under argon at room temperature did not afford any condensation product. Next, the starting compound **1** was mixed with 1.5 equiv of (±)-methylbenzylamine in dry toluene, with the addition of *p*-toluenesulfonic acid (PTSA) (10 mg, 0.06 mmol) under an argon atmosphere and the mixture was refluxed for 14 h using a Dean–Stark trap. After evaporation of the solvent in vacuo and purification of the crude product by flash column chromatography, a yellow oil (42%) was obtained, which proved to be *N*-(1-phenylethyl)-2-methyl-4,5,6,7-tetrahydroindole **2b**[10] instead of the anticipated enamine product (Scheme 1). Using this procedure we were also able to obtain the *N*-substituted 2-methyl-4,5,6,7-tetrahydroindole derivatives **2a**, **2c** and **2d** ('method A'). The results are given in Table 1. In entries 5–7 with aromatic amines, 'method A' failed to give the desired 2-methyl-4,5,6,7-tetrahydroindoles affording only the corresponding enamines. Using more than 0.1 equiv of PTSA resulted in formation of *p*-toluene sulfonate salts of the amine.

In order to complete the transformation of the enamines to the corresponding tetrahydroindole derivatives, we applied 'method B'.[11] In this method, the enamines were subsequently treated with potassium *tert*-butoxide in

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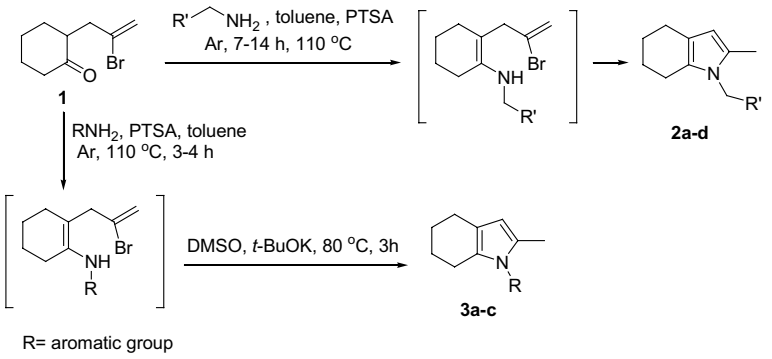
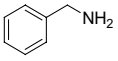
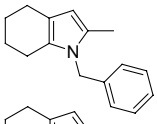
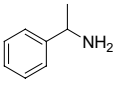
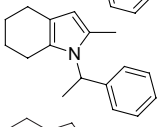
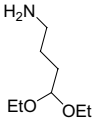
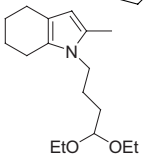
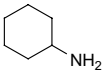
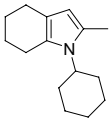
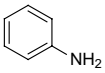
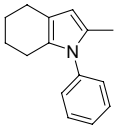
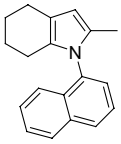
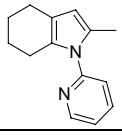


Scheme 1.

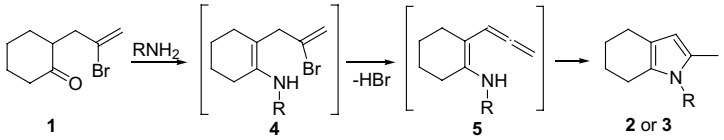
Table 1. Synthesis of *N*-substituted 4,5,6,7-tetrahydroindoles

Entry	Amine	Method	Product	**2** or **3**	Time (h)	Yield (%)
1		A		**2a**[8]	12	50
2		A		**2b**	14	42
3		A		**2c**	7	22
4		A		**2d**[13]	13	31
5		B		**3a**	7	98
6		B		**3b**	6	74
7		B		**3c**	6	72

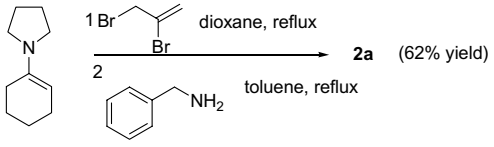
dimethyl sulfoxide to afford *N*-substituted 2-methyl-4,5,6,7-tetrahydroindole derivatives **3a**,[12] **3b** and **3c**.

The following mechanistic scheme is consistent with these results (Scheme 2). The reaction presumably proceeds through the formation of allenes **5** under basic conditions from the enamines **4**. The resultant intermediate **5** affords 2-methyl-4,5,6,7-tetrahydroindoles via a cyclization–aromatization reaction.

Yields using aromatic amines were much higher than with aliphatic amines. In order to increase the yield of tetrahydroindole formation from aliphatic amines, we tried to develop a transamination procedure. The reaction between freshly distilled 1-pyrrolidinyl-1-cyclohexene with 1 equiv of 2,3-dibromopropene in dioxane yielded a white waxy solid, which could not be characterized due to its sensitivity to air. Subsequently, this solid was reacted with 1.5 equiv of benzylamine, chosen as an example of a primary aliphatic amine, applying 'method A', hoping that the pyrrolidine would behave as a better leaving group than protonated oxygen. A 12% increase in yield was observed when compared with the reaction between **1** and benzylamine (Scheme 3).



Scheme 2.



Scheme 3.

In conclusion, we have demonstrated the versatility of 2-(2-bromoallyl)cyclohexanone **1** as a starting material for the one-pot synthesis of *N*-substituted 2-methyl-4,5,6,7-tetrahydroindoles. We have improved the yields from primary aliphatic amines by utilising a transamination procedure. In the future, we plan to use various chiral amines to afford the corresponding chiral *N*-substituted 2-methyl-4,5,6,7-tetrahydroindoles.

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References and notes

1. (a) Stetter, H.; Siehnhold, E. *Chem. Ber.* **1955**, *88*, 271; (b) Patterson, J. M.; Soedigdo, S. *J. Org. Chem.* **1967**, *32*, 2969; (c) Hershenson, F. M. *J. Org. Chem.* **1975**, *40*, 1260; (d) Dhanak, D.; Reese, C. B.; Romana, S.; Zappia, G. *J. Chem. Soc., Chem. Commun.* **1986**, *12*, 903; (e) Chelucci, G.; Gladiali, S.; Marchetti, M. *J. Heterocycl. Chem.* **1988**, *25*, 1761; (f) Enders, D.; Han, S. H.; Maaßen, R. *Tetrahedron Lett.* **1995**, *36*, 8007; (g) Lim, S.; Jabin, I.; Revial, G. *Tetrahedron Lett.* **1999**, *40*, 4177; (h) Ferraz, H. M. C.; Pereira, F. L. C.; Leita, F. M.; Nunes, M. R. S.; Payret-Arrua, M. E. *Tetrahedron* **1999**, *55*, 10915; (i) Ferraz, H. M. C.; Oliviera, E. O.; Payret-Arrua, M. E.; Brandt, C. A. *J. Org. Chem.* **1995**, *60*, 7357; (j) Mori, M.; Akashi, M.; Nishida, M. *Chem. Lett.* **1999**, 465; (k) Fukumoto, S.; Imamiya, E.; Kusumoto, K.; Watanabe, T.; Shiraishi, M. *J. Med. Chem.* **2002**, *45*, 3009; (l) Demir, A. S.; Akhmedov, İ. M.; Sesenoglu, O. *Tetrahedron* **2002**, *58*, 9793; (m) Mori, M.; Uozumi, Y.; Shibasaki, M. *Heterocycles* **1992**, *33*, 819.
2. Remers, W. A.; Weiss, M. J. *J. Org. Chem.* **1965**, *30*, 5232.
3. Masaguer, C. F.; Ravina, E. *Tetrahedron Lett.* **1996**, *37*, 5171.
4. (a) Sun, L.; Tran, N.; Liang, C.; Hubbard, S.; Tang, F.; Lipson, K.; Schreck, R.; Zhou, Y.; McMahon, G.; Tang, C. *J. Med. Chem.* **2000**, *43*, 2655; (b) Oba, T.; Tanaka, T.; Okamura, N.; Watanabe, K.; Bannai, K.; Ohtsu, A.; Naruchi, T.; Kurozumi, S.; Toru, T. *Eur. Pat. Appl.*, 1981, 145 pp; *Chem. Abstr.* **1981**, 95:24812.
5. McComas, C. C.; Van Vranken, D. L. *Tetrahedron Lett.* **1999**, *40*, 8039.
6. (a) O'Brien, S.; Smith, D. C. C. *J. Chem. Soc.* **1960**, 4609; (b) Young, D. V.; Snyder, H. R. *J. Am. Chem. Soc.* **1961**, *83*, 3160; (c) Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985**, *50*, 2962.
7. (a) De Kimpe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705; (b) Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Bon, Y. *J. Org. Chem.* **1983**, *48*, 4058.
8. Arcadi, A.; Rossi, E. *Tetrahedron* **1998**, *54*, 15253.
9. Nagano, H.; Ohtani, Y.; Odake, E.; Nakagawa, J.; Mori, Y.; Yajima, T. *J. Chem. Res. (S)* **1999**, *5*, 338.
10. Spectroscopic data for **2b** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.57–1.63 (m, 4H), 1.76 (d, J = 7.2 Hz, 3H), 2.02 (s, 3H), 2.41 (br s, 4H), 5.35 (q, J = 7.1 Hz, 1H), 5.62 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.14–7.25 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 143.1, 128.8, 127.7, 127.6, 127.2, 126.5, 116.8, 106.3, 52.8, 24.2, 24.1, 23.6, 20.0, 13.8, 1.4; MS(CI+): 240 ($[M+H]^+$, 100%), 238 (52%), 226 (11%); HRMS calcd for $C_{17}H_{22}N$ $(M+H)^+$, 240.1752. Found 240.1746.
11. General procedure for 'Method B: Starting compound **1** (0.31 g, 1.43 mmol) was mixed with 1.1 equiv of aniline (0.15 g, 1.57 mmol) in dry toluene (30 mL), with *p*-toluenesulfonic acid (10 mg, 0.06 mmol) under argon and the mixture was refluxed for 3 h using a Dean–Stark trap. After evaporation of the solvent in vacuo, dry dimethyl sulfoxide (3 mL) was added together with 1.1 equiv of potassium *tert*-butoxide (0.28 g, 2.46 mmol) and the reaction mixture was kept at 80 °C for 4 h. The reaction mixture was allowed to reach room temperature and purification by flash column chromatography afforded compound **3a** as a yellow oil (0.27 g, 98%).
12. Spectroscopic data for **3a** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.91 (t, J = 2.9 Hz, 4H), 2.24 (s, 3H), 2.49 (br s, 2H), 2.62 (br s, 2H), 5.99 (s, 1H), 7.37 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 139.3, 129.4, 128.5, 128.3, 127.7, 117.3, 106.3, 24.4, 24.1, 23.6, 23.5, 13.2.
13. For spectroscopic data of **2d** see: Ahlbrecht, H.; Von Daacke, A. *Synthesis* **1984**, *7*, 610.