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Tetrahedron Letters 45 (2004) 9541–9544

Tetrahedron Letters

$TiCl_4$/*t*-$BuNH_2$ as the sole catalyst for a hydroamination-based Fischer indole synthesis

Lutz Ackermann* and Robert Born

Department of Chemistry, Ludwig-Maximilians-Universität München, D-81377 München, Germany

Received 27 September 2004; revised 28 October 2004; accepted 29 October 2004
Available online 13 November 2004

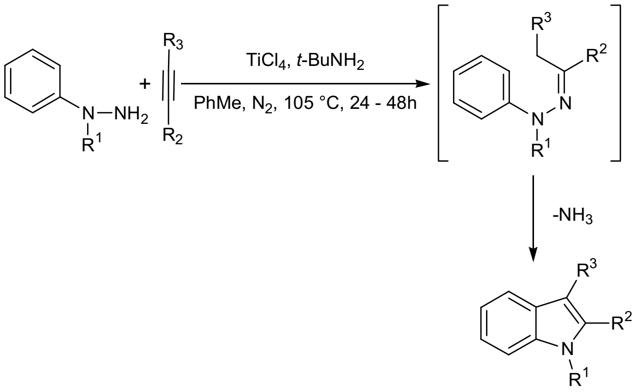
Abstract—A system comprising $TiCl_4$ and *t*-$BuNH_2$ acts as a catalyst for highly regioselective hydroamination reactions of alkynes using hydrazines and at the same time a Lewis acid in the transformation of the generated hydrazones into indole derivatives, while a 1,3-diyne is converted to pyrroles using the same precatalyst.

1. Introduction

The occurrence of the indole subunit in biologically active compounds has stimulated continued strong interest in practical syntheses of the indole scaffold.[1] Despite recently developed methodologies, such as palladium-catalyzed transformations,[2] the classical Fischer-indole cyclization[3] remains one of the most important approaches. Traditionally, the required hydrazones are generated via condensation of the corresponding carbonyl compound with a hydrazine derivative. Recently, Odom and co-workers presented an elegant, atom-economical approach to the indole framework based on intermolecular titanium[4] amide-catalyzed hydroamination reactions[1d,5] of alkynes with 1,1-disubstituted hydrazines, followed by a cyclization employing 3–5 equiv $ZnCl_2$.[6] Based on this methodology, Beller and co-workers described a one-pot tryptamine synthesis via hydroamination of terminal chloroalkylalkynes.[7] For the majority of substrate combinations, in particular internal alkynes, a subsequent addition of 3–5 equiv $ZnCl_2$ is necessary to convert the generated hydrazone into the corresponding indole.[6,7b] Recently, we reported procedures for the intermolecular hydroamination of alkynes[8] and norbornene,[9] using the inexpensive Lewis-acid $TiCl_4$ as the precatalyst. Consequently, we wondered if the addition of the Lewis-acid $ZnCl_2$ could be circumvented through the use of our $TiCl_4$-based methodology. Herein, we present a user-friendly system comprising commercially available $TiCl_4$ and *t*-$BuNH_2$ for the transformation of hydrazines and unsymmetrically substituted alkynes into indoles in a highly regioselective fashion.[10] Furthermore, the scope of a pyrrole synthesis based on a $TiCl_4$-catalyzed hydroamination of 1,3-diynes is evaluated.

2. Results and discussion

The system generated through the addition of *t*-$BuNH_2$ to a solution of $TiCl_4$ in toluene catalyzed the addition of 1,1-disubstituted hydrazines onto aryl- and alkyl-substituted alkynes efficiently (Scheme 1, Table 1).[11] For most examples the corresponding hydrazone was not observed according to GC/MS-analysis, but was directly



Scheme 1. $TiCl_4$/*t*-$BuNH_2$-catalyzed regioselective indole synthesis.

Keywords: Hydroamination; Indoles; Titanium.

* Corresponding author. Tel.: +49 89 2180 77675; fax: +49 89 2180 77425; e-mail: lutz.ackermann@cup.uni-muenchen.de

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doi:10.1016/j.tetlet.2004.10.160

Table 1. $TiCl_4$-catalyzed indole synthesis

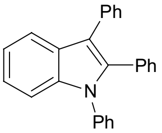
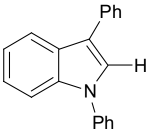
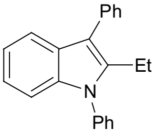
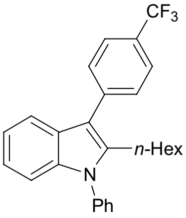
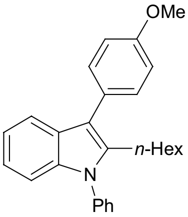
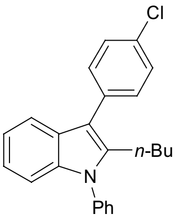
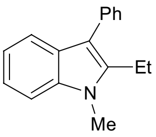
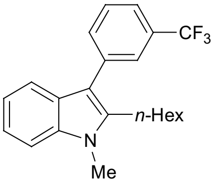
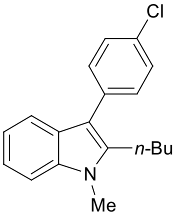
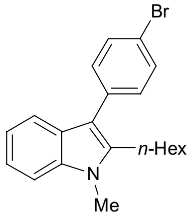
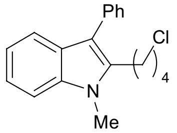
Entry		R^1	R^2	R^3	Product	Isolated yield[a] (%)
1	A	Ph	Ph	Ph		55
2	B	Ph	H	Ph		71[b]
3	A	Ph	Et	Ph		63[c]
4	B	Ph	*n*-Hex	$4\text{-}(CF_3)C_6H_4$		76
5	B	Ph	*n*-Hex	$4\text{-}MeOC_6H_4$		70
6	B	Ph	*n*-Bu	$4\text{-}ClC_6H_4$		62
7	A	Me	Et	Ph		73
8	C	Me	*n*-Hex	$3\text{-}(CF_3)C_6H_4$		71
9	C	Me	*n*-Bu	$4\text{-}ClC_6H_4$		57

Table 1 (*continued*)

Entry		R^1	R^2	R^3	Product	Isolated yield[a] (%)
10	C	Me	*n*-Hex	4-BrC_6H_4		66
11	C	Me	$(CH_2)_4Cl$	Ph		52

[a] Reaction conditions: 1.0 mmol alkyne, 1.0–3.0 mmol hydrazine, 2 mL PhMe, 24–48 h; A: 30 mol% $TiCl_4$, B: 40–50 mol% $TiCl_4$, C: 1.00 equiv $TiCl_4$.

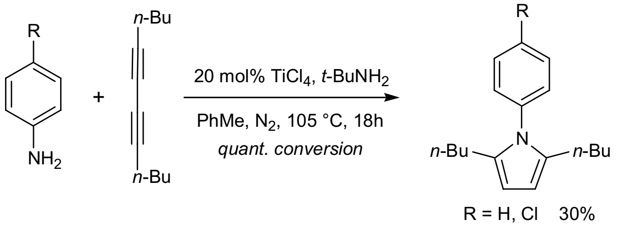
[b] At 75 °C.

[c] Using Ph_2NNH_3Cl.

converted to the indole derivative. While catalytic quantities of $TiCl_4$ were sufficient for quantitative conversion of alkynes using 1,1-diphenylhydrazine (entries 1–6), stoichiometric amounts proved beneficial for the synthesis of *N*-methyl substituted indoles (entries 8–11). Terminal alkynes were more reactive substrates, providing quantitative conversion of the alkyne even at 75 °C (entry 2).[12] Also a hydrazine hydrochloride gave the corresponding indole with good isolated yield through the use of an excess of *t*-$BuNH_2$ (entry 3).

The hydroamination of unsymmetrically substituted alkynes proceeded with excellent regioselectivity, giving rise to a single regioisomer as judged by GC/MS-analysis of the crude reaction mixture (entries 2–11). A variety of different functional groups, such as CF_3- (entries 4 and 8), MeO- (entry 5), Cl- (entries 6 and 9) and Br-substituents (entry 10) were tolerated, which enables further elaboration of the products. Interestingly, a chloroalkylalkyne proved compatible with our reaction conditions, without any evidence of nucleophilic substitution (entry 11).[7] Although dodeca-5,7-diyne was quantitatively converted under analogous reaction conditions, the corresponding *N*-phenyl-substituted indole was only isolated in a yield of 16%. We considered pyrrole formation via a sequence consisting of hydroamination and subsequent 5-*endo* cyclization as a potential reason for the low yield in the indole synthesis.

We probed our hypothesis by subjecting different aniline derivatives and dodeca-5,7-diyne to the reaction conditions (Scheme 2). With the in situ generated catalyst, the diyne was quantitatively converted at 105 °C.[13] Along with products stemming from hydroamination of both triple bonds, the corresponding pyrroles were formed as the major product and obtained in 30% isolated yield.[14]



Scheme 2. $TiCl_4$/*t*-$BuNH_2$-catalyzed pyrrole synthesis using a 1,3-diyne.

Acknowledgements

Generous support by the Ludwig-Maximilians-Universität, and Professor P. Knochel is gratefully acknowledged. We thank the DFG for financial support (Emmy Noether-Programm).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.160.

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11. A representative procedure is given for 2-ethyl-*N*-methyl-3-phenylindole (entry 7, Table 1): Under N_2, *N*-methyl-*N*-phenylhydrazine (390 mg, 3.18 mmol) was added in three portions to a solution of 1-phenyl-1-butyne (130 mg, 1.00 mmol), $TiCl_4$ (0.022 mL, 0.20 mmol, 20 mol%) and *t*-$BuNH_2$ (0.130 mL, 1.20 mmol) in toluene (2 mL). The resulting mixture was stirred for 40 h at 105 °C. CH_2Cl_2 (50 mL) and aq HCl (2 N, 50 mL) were added to the cold suspension. The separated aq phase was washed with CH_2Cl_2 (2×50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL). Drying with $MgSO_4$ and purification by column chromatography (silica gel, *n*-pentane/Et_2O 50/1 → 30/1) yielded 2-ethyl-*N*-methyl-3-phenylindole as a yellow solid (172 mg, 73%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (md, $J = 7.9$ Hz, 1H), 7.44–7.36 (m, 4H), 7.28–7.21 (m, 2H), 7.18–7.12 (m, 1H), 7.04 (ddd, $J = 8.0$ Hz, 7.1, 1.1 Hz, 1H), 3.70 (s, 3H), 2.81 (q, $J = 7.5$ Hz, 2H), 1.23 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0 (C_q), 136.7 (C_q), 135.8 (C_q), 129.7 (CH), 128.4 (CH), 127.2 (C_q), 125.8 (CH), 121.2 (CH), 119.6 (CH), 118.9 (CH), 113.7 (C_q), 108.8 (CH), 29.6 (CH_3), 18.1 (CH_2), 14.9 (CH_3). IR (KBr, cm^{-1}): 3054 (m), 2978 (m), 2933 (m), 1601 (m), 1470 (vs), 1371 (s), 775 (s), 744 (vs), 704 (vs). MS (EI) *m*/*z* (relative intensity) 235 ([M^+] 100), 220 (70), 204 (17), 179 (6). HR-MS (EI) *m*/*z* calcd for $C_{17}H_{17}N$ 235.1361, found 235.1355.
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