Tetrahedron Letters 51 (2010) 4560–4562

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Anhydrous $CeCl_3$ catalyzed C3-selective propargylation of indoles with tertiary alcohols

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ARTICLE INFO

Article history:
Received 21 May 2010
Revised 21 June 2010
Accepted 23 June 2010
Available online 27 June 2010

Keywords:
Indole
3-Propargyl indoles
Cerium(III) chloride

ABSTRACT

Anhydrous $CeCl_3$ was successfully used as catalyst for the synthesis of several 3-propargyl indoles in good yields through the reaction of indole with propargyl alcohols in nitromethane.

1. Introduction

Facile access to indole and their derivatives is of general interest since they are widely present in bioactive metabolites of numerous compounds isolated from natural sources.[1] Thus, the selective functionalization of indoles has attracted considerable attention.[2] From the synthetic point of view, the direct catalytic substitution of indoles with propargyl alcohols is a very interesting reaction due to the fact that water is the only by-product of the process.

Thus, several approaches for the preparation of 3-propargyl indoles have been described in recent years. The most useful approaches are based on transition-metal,[3] Lewis[4] and Brønsted acid[5] catalyzed methodologies for the direct substitution reaction of alcohols with indoles. However, major drawbacks are still present such as accessibility, substrate compatibility and stability of these reagents. Hence, a mild general approach for the 3-propargylation of indoles is still necessary.

Cerium(III) chloride has emerged as a very useful Lewis acid imparting high regio- and chemoselectivity in various chemical transformations over the past few years. It is an inexpensive, nontoxic and water-tolerant catalyst and has been used in several different forms, alone as heptahydrate, anhydrous, and in combination with NaI.[6] The salt has also been used in solid supports,[7] which modify its reactivity. Organocerium compounds also find extensive use in organic synthesis.[8]

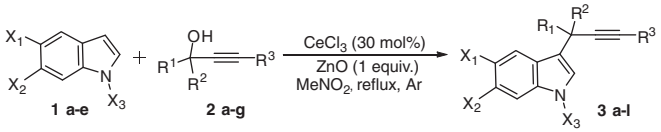
In view of our interest in the development of new, cleaner methods for classical reactions promoted by cerium(III) species,[9] we decided to study the electrophilic substitution reaction of indoles (**1**) with propargyl alcohols (**2**) to obtain 3-propargyl indoles (**3**, Scheme 1).

2. Results and discussion

Initially, we chose indole and 2,4-diphenylbut-3-yn-2-ol (**2a**) as the starting materials to establish the best conditions for the reaction. At first, we found that by using 0.3 equiv of $CeCl_3$ in MeCN, the 3-propargyl indole (**3a**) was obtained in 10% yield after stirring under reflux for 5 h (Table 1, entry 1). We employed other solvents, such as glycerin, DMA, *i*-PrOH and $MeNO_2$ (Table 1, entries 2–5). The best yield was obtained with $MeNO_2$ (60% isolated yield; Table 1, entry 5).

The use of larger amounts of $CeCl_3$ had no effect on the yield of the reaction and the time to completion of the reaction was the same (Table 1, entry 6). However, when 0.1 equiv of dry $CeCl_3$ was used, 25% of **3a** was obtained (Table 1, entry 7). Replacing anhydrous $CeCl_3$ with $CeCl_3{\cdot}7H_2O$, gave no product (Table 1, entry 8).

In a search for an even higher yield, we decided to employ ZnO as an additive, due to the fact that metal–oxides were described as a convenient and practical base that forms a strong metal–nitrogen



Scheme 1.

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doi:10.1016/j.tetlet.2010.06.112

Table 1
Optimization of conversion of **1a**–**3a**[a]

Entry	Solvent	$CeCl_3$ (equiv)	ZnO (equiv)	Temp (°C)	Time (h)	Yield (%)
1	MeCN	0.3	—	Reflux	5	10
2	Glycerin	0.3	—	90	5	—[b]
3	DMA	0.3	—	100	5	—[b]
4	*i*-PrOH	0.3	—	Reflux	3	49
5	$MeNO_2$	0.3	—	Reflux	3	60
6	$MeNO_2$	0.5	—	Reflux	3	60
7	$MeNO_2$	0.1	—	Reflux	3	25
8	$MeNO_2$	0.3[c]	—	Reflux	5	—[b]
9	$MeNO_2$	0.3	1.0	Reflux	2	87
10	$MeNO_2$	0.2	1.0	Reflux	5	68
11	$MeNO_2$	0.5	1.0	Reflux	2	86
12	$MeNO_2$	—	1.0	Reflux	5	—[b]
13	$MeNO_2$	0.3	0.5	Reflux	3	69
14	$MeNO_2$	0.3	1.0	65	6	84

[a] Reaction conditions: indole (**1a**, 1.0 mmol); 2,4-diphenylbut-3-yn-2-ol (**2a**, 1.1 mmol), and solvent (2 mL).
[b] No reaction.
[c] Reaction performed with $CeCl_3 \cdot 7H_2O$.

bond and may increase the nucleophilicity of the annular carbon centers of the heteroarene.[10] The reaction was carried out with ZnO (1 equiv) and $CeCl_3$ (30 mol %) in $MeNO_2$, which increased the product yield to 87% after 2 h (Table 1, entry 9).

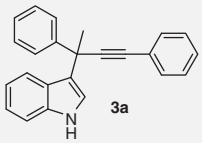
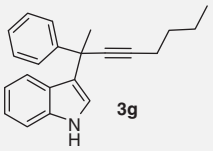
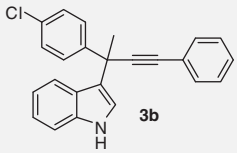
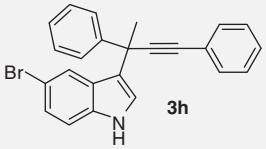
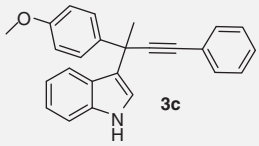
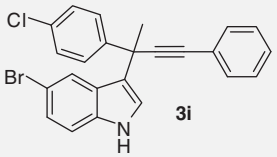
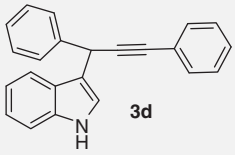
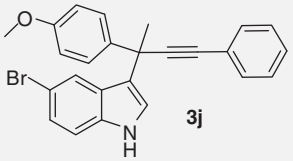
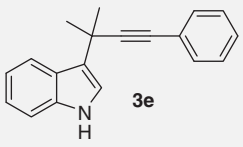
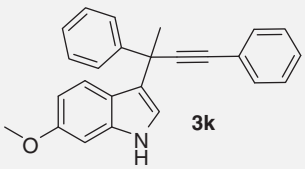
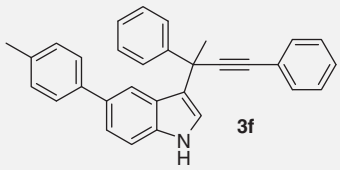
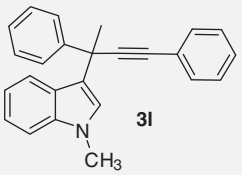
Then, the effect of the amounts of the zinc oxide and cerium chloride was evaluated. When the reaction was performed with 1 equiv of ZnO in the absence of $CeCl_3$, no product was obtained (Table 1, entry 12); however, employing 30 mol % of $CeCl_3$ gave the best conversions. Lowering the reaction temperature to 65 °C (oil bath temperature) furnished very similar product yields, but a longer reaction time was required (6 h, Table 1, entry 14).

Thus, the best conditions for the C3-selective propargylation of indoles with tertiary alcohols were the use of $CeCl_3$ (0.3 mmol), ZnO (1.0 mmol), indole (1.0 mmol), propargyl alcohol (1.1 mmol), in refluxing $MeNO_2$ (2 mL), under argon (Scheme 1).[11]

With these optimized conditions in hand, we next extended the transformation to some other examples in order to find out the scope and limitations of the present method. (Table 2, Scheme 1).[11] For almost all the studied examples, the 3-propargyl indoles **3** were obtained in good yields after stirring at reflux temperature for 2–3 h (Table 2).

The exceptions were observed when secondary and dimethyl alcohols were used, which furnished the products **3d** and **3e** in lower yields (Table 2, entries 4 and 5). Also, the use of an hexyne derivative gave lower yield of product **3g** which was observed, as a consequence of the lower stabilization of the charged intermedi-

Table 2
Synthesis of 3-propargyl indoles **3**

Entry	Product **3**	Time (h)	Yield[a] (%)	Entry	Product **3**	Time (h)	Yield[a] (%)
1	 **3a**	2	87	7	 **3g**	3	55
2	 **3b**	2	78	8	 **3h**	2	88
3	 **3c**	2	85	9	 **3i**	2	80
4	 **3d**	12	41	10	 **3j**	2	82
5	 **3e**	12	28	11	 **3k**	2	79
6	 **3f**	2	72	12	 **3l**	3	71

[a] Yields of pure products isolated by column chromatography (hexanes/AcOEt, 98:2) and identified by GC–MS, ^1H and ^{13}C NMR.

ate compared to a phenyl group on the propargylic alcohol. When 5-bromo-1*H*-indole was used, the respective brominated products were obtained with yields compared to indole (Table 2, entries 8–10).

It is worth mentioning that the indole nitrogen does not require protection. Nevertheless, we also performed the transformation with a nitrogen protected indole derivative. When the reaction was carried out with 1-methyl-1*H*-indole and 2,4-diphenylbut-3-yn-2-ol and in the presence of ZnO, the corresponding product **3l** was obtained in 71% yield after 3 h. Since in this case no N–H bond is present, the same reaction was also performed in the absence of ZnO. However, reduced yields were observed (64%, mean of three reactions), indicating that the beneficial effect of ZnO is still present. However, when 1-tosyl-1*H*-indole was used, no reaction was observed even after several hours of reaction, presumably as a consequence of the deactivation effect of the tosyl group.

In conclusion, we have described a convenient method for the preparation of 3-propargyl indoles from the propargyl alcohols in a reaction mediated by cerium(III) chloride. The method is simple, general and the products are obtained in good yields.

Acknowledgments

This project was funded by MCT/CNPq, and CAPES. G.M.M. thanks FAPERGS for an undergraduate fellowship.

References and notes

1. (a) Sundberg, R. J. In *The Chemistry of Indoles*; Academic Press: New York, 1996; (b) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C. O.; Sim, C. J.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **2005**, *68*, 711; (c) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. *J. Nat. Prod.* **2000**, *63*, 447; (d) Garbe, T. R.; Kobayashi, M.; Shimizu, N.; Takesue, N.; Ozawa, M.; Yukawa, H. *J. Nat. Prod.* **2000**, *63*, 596.
2. (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608; (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875; (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873; (d) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199.
3. (a) Georgy, M.; Boucard, V.; Debleds, O.; Dal Zotto, C.; Campagne, J.-M. *Tetrahedron* **2009**, *65*, 1758; (b) Kanao, K.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Synthesis* **2008**, 3869; (c) Zaitsev, A. B.; Gruber, S.; Pregosin, P. S. *Chem. Commun.* **2007**, 4692; (d) Whithney, S.; Grigg, R.; Derrick, A.; Keep, A. *Org. Lett.* **2007**, *9*, 3299; (e) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561; (f) Inada, Y.; Yoshikawa, M.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Eur. J. Org. Chem.* **2006**, 881; (g) Kennedy-Smith, J. J.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325.
4. (a) Yadav, J. S.; Subba Reddy, B. V.; Raghavendra Rao, K. V.; Narayana Kumar, G. G. K. S. *Tetrahedron Lett.* **2007**, *48*, 5573; (b) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2007**, *48*, 7160; (c) Yadav, J. S.; Subba Reddy, B. V.; Raghavendra Rao, K. V.; Narayana Kunar, G. G. K. S. *Synthesis* **2007**, 3205; (d) Srihari, P.; Bhunia, D. C.; Sreedhar, P.; Mandal, S. S.; Shyam Sunder Reddy, J.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 8120.
5. (a) Sanz, R.; Gohain, M.; Miguel, D.; Martínez, A.; Rodríguez, F. *Synlett* **2009**, 1985; (b) Sanz, R.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Synlett* **2008**, 975; (c) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 311; (d) Motokura, K.; Nakagiri, N.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **2007**, *72*, 6006; (e) Le Bras, J.; Muzart, J. *Tetrahedron* **2007**, *63*, 7942.
6. (a) Sabitha, G.; Yadav, J. S In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley-VCH: Weinheim, 2006; (b) Bartoli, G.; Di Antonio, G.; Giovannini, R.; Giuli, S.; Lanari, S.; Paoletti, M.; Marcantoni, E. *J. Org. Chem.* **2008**, *73*, 1919; (c) Yadav, J. S.; Subba Reddy, B. V.; Suresh Reddy, Ch.; Krishna, A. D. *Tetrahedron Lett.* **2007**, *48*, 2029; (d) Meng, Q.; Sun, Y.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Zhang, Z. *J. Org. Chem.* **2008**, *73*, 3842.
7. (a) Ahmed, N.; Van Lier, J. E. *Tetrahedron Lett.* **2007**, *48*, 13; (b) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941; (c) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169; (d) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594.
8. (a) Bartoli, G.; Belluci, M. C.; Bosco, M.; Dalpozzo, R.; De Nino, A.; Sambri, L.; Tagarelli, A. *Eur. J. Org. Chem.* **2000**, 99; (b) Liu, H. J.; Shia, K. S.; Shang, X.; Zhu, B. Y. *Tetrahedron* **1999**, *55*, 3803.
9. (a) Silveira, C. C.; Mendes, S. R.; Wolf, L.; Martins, G. M. *Tetrahedron Lett.* **2010**, *51*, 2014; (b) Silveira, C. C.; Mendes, S. R.; Libero, F. M. *Synlett* **2010**, 790; (c) Silveira, C. C.; Mendes, S. R.; Ziembowicz, F. I.; Lenardão, E. J.; Perin, G. *J. Braz. Chem. Soc.* **2010**, *21*, 371; (d) Silveira, C. C.; Mendes, S. R.; Libero, F. M.; Lenardão, E. J.; Perin, G. *Tetrahedron Lett.* **2009**, *50*, 6060; (e) Silveira, C. C.; Mendes, S. R.; Rosa, D. D.; Zeni, G. *Synthesis* **2009**, 4015; (f) Silveira, C. C.; Mendes, S. R. *Tetrahedron Lett.* **2007**, *48*, 7469.
10. (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050; (b) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580; (c) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274.
11. *General procedure for the synthesis of 3-propargyl indoles*: To a mixture of $MeNO_2$ (2 mL), indole (**1**, 1.0 mmol) and propargyl alcohol (**2**, 1.1 mmol), under Ar, was added anhydrous $CeCl_3$ (0.072 g, 0.3 mmol) and ZnO (0.081 g, 1.0 mmol). The reaction mixture was then heated under reflux for the time indicated in Table 2. The reaction mixture was followed by TLC. Next, the reaction mixture was cooled to rt and water (20 mL) was added. The mixture was extracted with ethyl acetate (3 × 10 mL), the organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (ethyl acetate–hexanes, 02:98) to afford pure products (**3a**–**l**). Spectral data of selected compounds: **3a**:[5b] mp 32–35 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77 (br s, 1H), 7.60–6.92 (m, 15 H), 2.07 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.1, 137.0, 131.6, 128.1, 127.7, 126.5, 126.4, 125.9, 125.6, 123.7, 121.9, 121.5, 121.0, 119.2, 111.1, 95.0, 83.0, 68.9, 39.8, 31.0. MS: *m/z* (%) 321 (M^+, 69), 306 (100), 244 (18), 152 (19); **3l**:[5b] ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.62–6.92 (m, 15H), 3.71 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.2, 137.8, 131.6, 129.0 (2C), 127.6, 126.6, 126.4, 126.2, 126.1, 123.9, 121.5, 121.2, 120.2, 118.8, 109.1, 95.2, 83.0, 39.8, 32.7, 31.0. MS: *m/z* (%) = (M^+, 60), 320 (100), 258 (17), 159 (18), 127 (7), 77 (4).