Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 3295–3298
Tetrahedron Letters

$Dy(OTf)_3$ as a versatile catalyst for the synthesis of 3-pyrrolyl-indolinones and pyrrolyl-indeno[1,2-*b*]quinoxalines

J. S. Yadav,* B. V. Subba Reddy, Ruchi Jain and Ch. Suresh Reddy

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

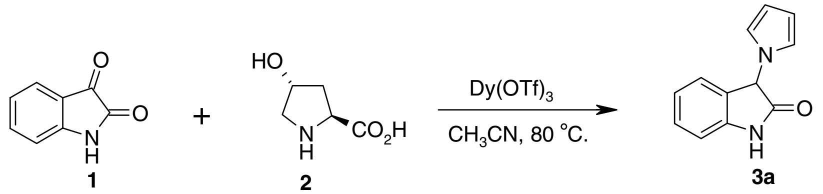
Received 4 January 2007; revised 21 February 2007; accepted 28 February 2007
Available online 3 March 2007

Abstract—Dysprosium(III) triflate is found to catalyze efficiently the coupling of 4-hydroxyproline with indeno[1,2-*b*]quinoxalin-11-one and isatin derivatives under mild conditions to produce 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalin-11-one and 3-(1*H*-pyrrol-1-yl)indolin-2-one derivatives, respectively, in excellent yields in short reaction times. A comparative study with both $InCl_3$ and $Dy(OTf)_3$ is described.

Pyrrole derivatives are important intermediates for the synthesis of drugs, pigments and pharmaceuticals and for the development of organic functional materials.[1] They are found in many naturally occurring compounds such as heme, chlorophyll, and vitamin B_{12}.[2] They are also present in various bioactive drug molecules such as atrovastatin, anti-inflammatory and antitumor agents, and immunosuppressants.[3] Consequently, a variety of synthetic methods for the preparation of pyrrole derivatives have been reported in the literature.[3,4] Among them, the Paal–Knorr reaction remains one of the most attractive methods for the synthesis of pyrroles.[5] However, many of the classical methods often involve the use of stoichiometric amounts of reagents, extended reaction times and also generate mixtures of products.[3] Consequently, new catalytic systems are being explored in the search for improved efficiencies.[6] Since indolinone and quinoxaline systems are useful and important in the field of drugs and pharmaceuticals, the development of simple, convenient and high yielding protocols is desirable.

Lanthanide triflates are Lewis acids that are currently of great research interest. They are highly oxophilic and form strong, but labile bonds with oxygen donor ligands. This feature has often allowed sub-stoichiometric amounts of these Lewis acids to be used to promote a variety of reactions.[7] Indeed, such Lewis acids are found to be effective in promoting many organic transformations. However, the use of dysprosium triflate as a catalyst in organic synthesis is scarce.[8]

In continuation of our interest on the catalytic applications of lanthanide triflates as water-tolerant and recyclable Lewis acids in carbon–carbon bond forming reactions,[9] we report herein an efficient synthesis of N-substituted pyrroles attached to an indole skeleton by the coupling of 4-hydroxyproline with isatins under



Scheme 1.

Keywords: Pyrrole; Isatins; Lanthanide triflate; Indolinone; Quinoxaline.

* Corresponding author. Fax: +91 40 27160512; e-mail: yadavpub@iict.res.in

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.02.134

neutral conditions. Accordingly, treatment of isatin (**1**) with 4-hydroxyproline (**2**) in the presence of Dy(OTf)$_3$ in acetonitrile at 80 °C for 20 min gave the corresponding 3-(1*H*-pyrrol-1-yl)indolin-2-one (**3a**) in 94% yield (Scheme 1).

Similarly, a variety of isatin derivatives such as 1-methylisatin, 5-bromo-1-methylisatin, 5-cyanoisatin, 1-benzyl-5-cyanoisatin, 1-benzyl-5-nitroisatin, and 5,7-dibromoisatin underwent smooth coupling with 4-hydroxyproline to give the corresponding 3-(1*H*-pyrrol-1-yl)indolin-2-ones in good to excellent yields (Table 1, entries b–g). Thus, this method is very useful for the preparation of N-substituted pyrroles from isatin derivatives. Interestingly, 7-aza-isatin derivatives such as 1-benzyl-7-aza-isatin and 1-ethyl-7-aza-isatins also gave the corresponding 3-pyrrolyl-7-aza-indolinones in high yields (Table 1, entries h and i). Encouraged by the results obtained with isatin derivatives, we turned our attention to 11*H*-indeno[1,2-*b*]quinoxalin-11-one derivatives. Interestingly, 11*H*-indeno[1,2-*b*]quinoxalin-11-ones underwent smooth coupling with 4-hydroxyproline

Table 1. Preparation of 3-(1*H*-pyrrol-1-yl)indolin-2-ones and 11-(1*H*-pyrrol-1-yl)11-*H*-indeno[1,2-*b*]quinoxalines

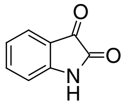
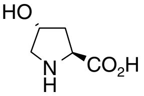
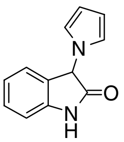
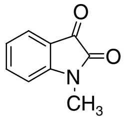
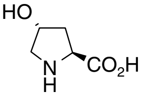
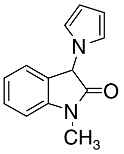
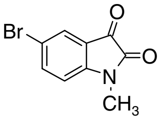
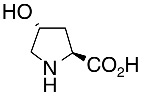
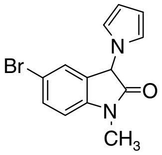
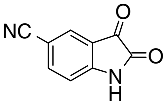
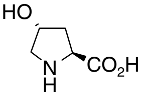
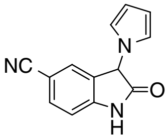
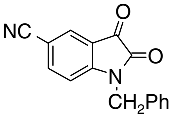
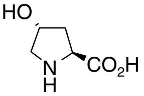
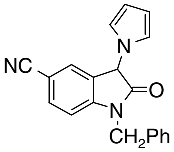
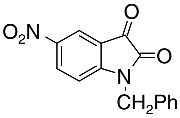
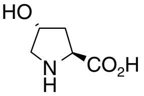
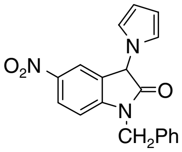
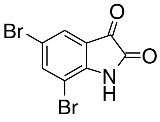
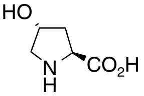
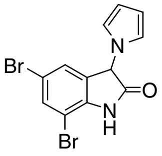
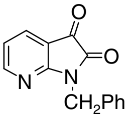
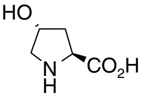
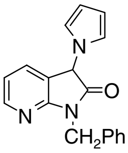
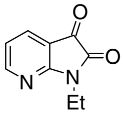
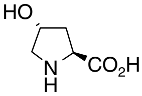
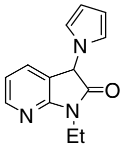
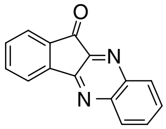
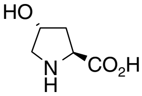
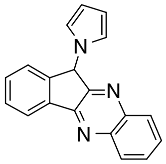
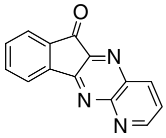
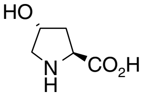
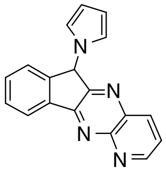
Entry	Substrate	4-Hydroxyproline	Product[a]	InCl$_3$		Dy(OTf)$_3$	
				Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
a				30	90	20	94
b				25	92	15	98
c				40	78	25	90
d				50	79	38	89
e				60	80	32	90
f				75	82	40	84
g				90	60	65	70
h				70	85	56	89

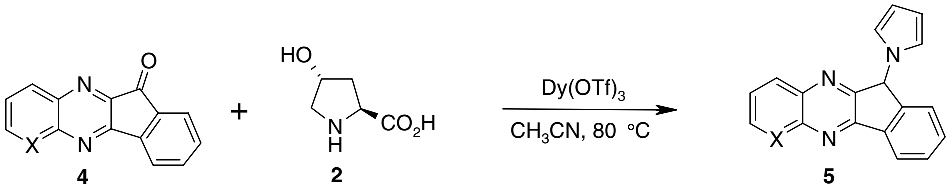
Table 1 (*continued*)

Entry	Substrate	4-Hydroxyproline	Product[a]	$InCl_3$		$Dy(OTf)_3$	
				Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
i				80	87	68	90
j				120	71	100	80
k				180	79	140	82

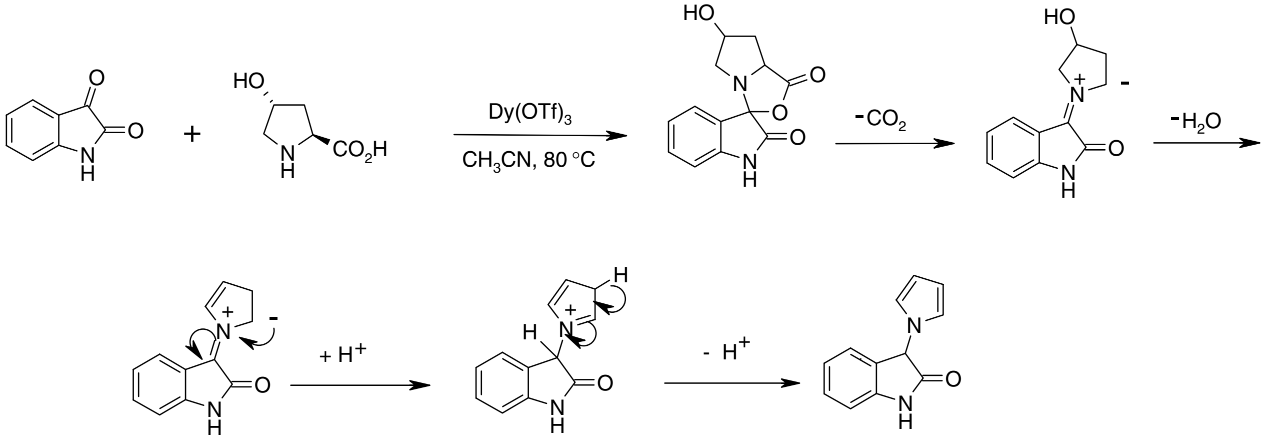
[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b] Isolated and unoptimized yield.

under similar conditions to produce the corresponding 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalin-11-ones **5** in good yields (Scheme 2 and Table 1, entries j and k).

However, no reaction was observed in the absence of catalyst even after a long reaction time (12 h). Although the reactions worked well in water, they took a longer time to give comparable yields. As solvent, acetonitrile appeared to give the best results. In all cases, the reactions proceeded rapidly under mild conditions. The reactions were clean and the products were obtained in excellent yields. The structures of the products were established by ^{1}H NMR and also by comparison with authentic samples.[5] The formation of the products may be explained by the formation of an azomethine ylide via decarboxylation and a subsequent 1,5-proton shift to generate the more stable zwitterion as shown in Scheme 3.



Scheme 2.



Scheme 3.

However, simple 1,2-diketones such as benzil and acenaphthenequinone failed to produce the desired product under the same reaction conditions. This method works only with substrates possessing α-ketoamido and α-ketoimino functionalities due to the stabilization of the zwitterionic intermediate during the reaction. Among various rare earth metal triflates such as Y(OTf)$_3$, Ce(OTf)$_3$, Sm(OTf)$_3$, and Gd(OTf)$_3$ tested, Dy(OTf)$_3$ was found to be most efficient in terms of conversion. Although, InCl$_3$ was shown to be equally effective for this transformation, it is more expensive than Dy(OTf)$_3$. The nature of the substituents on the aromatic ring shows some effect on this conversion. It should be noted that simple aromatic and moderately activated isatins gave higher yields of products compared to strongly deactivated substrates (Table 1). The scope and generality of this process is illustrated with respect to various isatin derivatives and the results are presented in Table 1.[10]

In summary, we have described a novel and efficient protocol for the preparation of 3-(1*H*-pyrrol-1-yl)indolin-2-ones from 4-hydroxyproline and isatins using Dy(OTf)$_3$ or InCl$_3$. In addition to its simplicity and mild reaction conditions, this method offers high yields of products in short reaction times. This method provides an easy access to the synthesis of 3-(1*H*-pyrrol-1-yl)indolin-2-one and 11-(1*H*-pyrrol-1-yl)-11*H*-indeno-[1,2-*b*]quinoxalin-11-one derivatives in a single-step reaction.

Acknowledgment

R.J. and Ch.S.R. thank the CSIR, New Delhi for the award of fellowships.

References and notes

1. (a) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977; pp 1–5; (b) Lainton, J. A. H.; Hoffman, J. W.; Martin, B. R.; Compton, D. R. *Tetrahedron Lett.* **1995**, *36*, 1401.
2. (a) De Leon, C. Y.; Ganem, B. *Tetrahedron* **1997**, *53*, 7731; (b) Di Santo, R.; Costi, R.; Artico, M.; Massa, S.; Lampis, G.; Deidda, D.; Rompei, R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2931; (c) Ragno, R.; Marshall, G. R.; Di Santo, R.; Costi, R.; Massa, S.; Rompei, R.; Artico, M. *Bioorg. Med. Chem. Lett.* **2000**, *8*, 1423.
3. (a) Thompson, R. B. *FASEB J.* **2001**, *15*, 1671; (b) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109; (c) Cozzi, P.; Mongelli, N. *Curr. Pharm. Des.* **1998**, *4*, 181; (d) Furstner, A.; Thompson, R. B. *FASEB J.* **2001**, *15*, 1671; (e) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109; (f) Cozzi, P.; Mongelli, N. *Curr. Pharm. Des.* **1998**, *4*, 181; (g) Furstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305.
4. (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615, and references cited therein; (b) Yu, S.-X.; Le Quesne, P. W. *Tetrahedron Lett.* **1995**, *36*, 6205.
5. (a) Paal, C. *Chem. Ber.* **1884**, *17*, 2756; (b) Knorr, L. *Chem. Ber.* **1884**, *17*, 2863.
6. (a) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *J. Org. Chem.* **2005**, *70*, 1471; (b) Banik, B. K.; Cardona, M. *Tetrahedron Lett.* **2006**, *47*, 7385.
7. (a) Kobayashi, S. *Synlett* **1994**, 689; (b) Kobayashi, S. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 370; (c) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15; (d) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994.
8. (a) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *J. Chem. Soc., Chem. Commun.* **1999**, 651; (b) Batey, R. A.; Powell, D. A.; Acton, A.; Lough, A. J. *Tetrahedron Lett.* **2001**, *42*, 7935.
9. (a) Yadav, J. S.; Reddy, B. V. S.; Rao, T. P. *Tetrahedron Lett.* **2000**, *41*, 7943; (b) Yadav, J. S.; Reddy, B. V. S.; Chandrasekhar, K. *Tetrahedron Lett.* **2001**, *42*, 4405; (c) Yadav, J. S.; Reddy, B. V. S.; Chand, P. K. *Tetrahedron Lett.* **2001**, *42*, 4057; (d) Yadav, J. S.; Reddy, B. V. S.; Srihari, P. *Synlett* **2001**, 673; (e) Yadav, J. S.; Reddy, B. V. S.; Reddy, J. S. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2390.
10. *General procedure*: A mixture of 4-hydroxyproline (1 mmol), isatin (1 mmol), and Dy(OTf)$_3$ or InCl$_3$ (0.1 mmol) in acetonitrile (5 mL) was stirred at 80 °C for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) gave pure 3-(1*H*-pyrrol-1-yl)indolin-2-one. The products thus obtained were characterized by IR, NMR, and mass spectroscopy. The characterization data were found to be consistent with authentic samples.[6] Compound **3f**: 1-Benzyl-5-nitro-3-(1*H*-pyrrol-1-yl)indolin-2-one: solid, mp 123–126 °C; IR (KBr): (ν_{max}): 2924, 2853, 1738, 1614, 1521, 1487, 1336, 1074, 729 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.24 (d, $J = 8.3$ Hz, 1H), 8.16 (m, 1H), 7.32 (m, 5H), 6.85 (d, $J = 9.0$ Hz, 1H), 6.62 (t, $J = 2.2$ Hz, 2H), 6.23 (t, $J = 1.5$ Hz, 2H), 5.59 (s, 1H), 4.95 (q, $J = 15.8$ Hz, 2H). LC–MS: *m*/*z*: 333.1 (M). $^+$HRMS calcd for C$_{19}$H$_{15}$N$_3$O$_3$Na: 356.1011. Found: 356.1007. Compound **3h**: 1-Benzyl-(1*H*-pyrrol-1-yl)-1*H*-pyrrol[2,3-*b*]pyridin-2-[3*H*]-one: solid, mp 125–128 °C; IR (KBr): (ν_{max}): 2924, 2853, 1727, 1623, 1460, 1337, 1258, 1079, 741 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.27 (d, $J = 8.4$ Hz, 1H), 7.51–7.43 (m, 3H), 7.30–7.22 (m, 3H), 6.98 (dd, $J = 5.3$, 7.2 Hz, 1H), 6.55 (d, $J = 2.1$ Hz, 2H), 6.22 (t, $J = 2.1$ Hz, 2H), 5.44 (s, 1H), 4.96 (q, $J = 14.2$ Hz, 2H). LC–MS: *m*/*z*: 290 (M+1). $^+$HRMS calcd for C$_{18}$H$_{15}$N$_3$ONa: 312.1112. Found: 312.1104. Compound **5k**: 6-(1*H*-1-Pyrroyl)-6*H*-indeno-[1,2-*b*]-pyrido[3,2-*e*]pyrazine: solid, mp 150–153 °C; IR (KBr): (ν_{max}): 2959, 2927, 2854, 1725, 1577, 1283, 1076, 787 cm^{-1}. ^{1}H NMR (CDCl$_3$, 200 MHz): δ 9.12 (s, 1H), 8.38 (m, 1H), 7.70–7.61 (m, 4H), 7.52–7.47 (m, 1H), 6.67 (t, $J = 1.5$ Hz, 2H), 6.18 (t, $J = 1.5$ Hz, 2H), 6.15 (s, 1H). LC–MS: *m*/*z*: 285 (M+1). $^+$HRMS calcd for C$_{18}$H$_{12}$N$_4$Na: 307.0959. Found: 307.0981.