Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron

Tetrahedron 61 (2005) 6425–6437

A highly active catalyst for the reductive cyclization of *ortho*-nitrostyrenes under mild conditions

Ian W. Davies,* Jacqueline H. Smitrovich,✠ Rick Sidler, Chuanxing Qu, Venita Gresham and Charles Bazaral

Department of Process Research, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065-0900 USA

Received 1 November 2004; revised 28 February 2005; accepted 4 March 2005

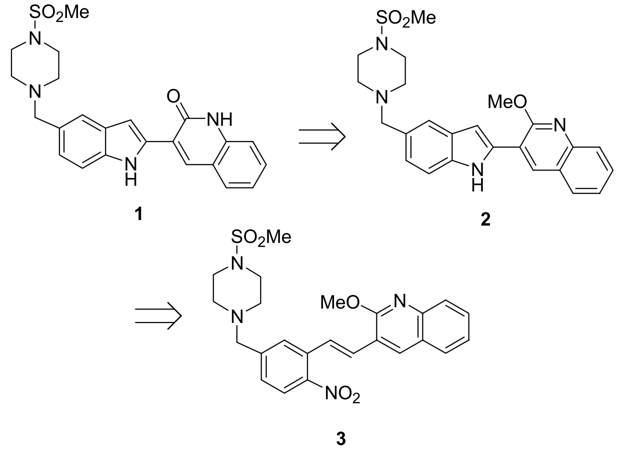
Dedicated to the memory of Jackie Smitrovich – a dear friend and a talented colleague

Abstract—A mild and efficient method for the palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes to afford indoles is reported. Treatment of *ortho*-nitrostyrenes with 0.1 mol% palladium (II) trifluoroacetate [Pd(TFA)$_2$] and 0.7 mol% 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF at 15 psig CO and 80 °C afforded indoles in good to excellent yields. When the reaction was conducted in toluene, the corresponding *N*-hydroxyindole was isolated. A mechanism that accounts for the formation of *N*-hydroxyindole is proposed.

1. Introduction

Substituted indoles are privileged structures[1] that are present in a wide range of pharmacophores.[2] As such, the synthesis of indoles represents a long and rich area of synthetic organic chemistry.[3] KDR kinase inhibitor **1** was identified as part of Merck's efforts[4] for blocking tumor-induced angiogenesis.[5] Due to the low solubility of **1** imparted by the quinilone ring, we proposed unmasking the quinolone in the final step, making methoxy-protected **2** our synthetic target (Scheme 1). Of the synthetic approaches investigated,[6] construction of the indol-2-yl methoxyquinoline core of **2** by reductive cyclization of *ortho*-nitrostyrene **3** was appealing in that this substrate could be convergently assembled in a short number of steps.[7] This strategy would require a mild method for the reductive cyclization.

The Cadogan deoxygenation of nitroaromatics using boiling triethyl phosphite is now a classic synthetic method for the construction of a wide range of nitrogen-containing aromatic heterocycles and remains the most common method to affect deoxygenative cyclization.[8,9] While broad in scope, the generation of a large amount of phosphorous waste detracts from this approach. Transition metal promoted deoxygenation of nitroaromatics to give heterocycles was first realized by Waterman and Vivian in 1940 using stoichiometric iron oxalate at 200 °C.[10] In recent years, transition metal catalyzed variants of this reaction using CO as the stoichiometric reductant have been developed,[11] however, the moderate yields and extreme conditions (1175 psi CO and 220 °C) significantly limit the synthetic utility of this system. Palladium-based systems have subsequently been identified as more efficient catalysts for this transformation. The palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes in the presence of stoichiometric SnCl$_2$ at 100 °C and 275 psi CO was developed by Watanabe.[12] Söderberg reported a Pd/triphenylphoshphine system effective at



Scheme 1.

Keywords: Nitrostyrene; Reductive cyclization; Palladium.

* Corresponding author. E-mail: ian_davies1@merck.com

✠ Deceased.

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.142

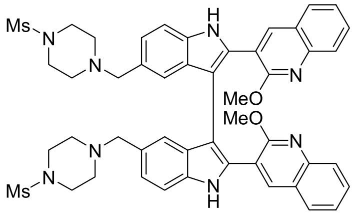
Table 1. Reductive cyclization of **3** using Pd(OAc)$_2$/triphenylphosphine

$$\mathbf{3} \xrightarrow[\text{CO, ACN}]{\text{Pd(OAc)}_2\text{, PPh}_3} \mathbf{2}$$

Entry	Pd(OAc)$_2$ (mol%)	PPh$_3$ (mol%)	CO (psig)	Temp (°C)	2 (% yield)[a]
1	6	24	60	70	95 (45)[b]
2	6	24	60	40	32
3	6	24	30	70	90
4	6	24	15	70	50
5	2	4	60	70	71
6	1	2	60	70	63

[a] HPLC assay yield.

[b] Yield reported for material isolated by crystallization.



4

Figure 1.

lower temperatures and pressures (70 °C and 60 psi) at 6 mol% palladium loading.[13] Catalysts derived from palladium(II) salts and bidentate nitrogen ligands effect cyclization of *ortho*-nitrostyrenes at low catalyst loading, however, these reactions require harsh conditions (300 psi CO and 120 °C).[14] Catalytic alternatives effective at mild temperatures and pressures would enhance widespread uptake of this technology. Our approach to developing a highly efficient catalytic system relied upon systematic screening using a 6×8 parallel Parallel Pressure Reactor (PPR®). Results of these studies and investigations into the reaction mechanism are presented herein.

2. Results and discussion

The relatively mild pressure and temperature required for Pd/phosphine catalytic systems motivated us to apply this system towards the reductive cyclization of **3**. Using the conditions reported by Söderberg [6 mol% Pd(OAc)$_2$, 24 mol% PPh$_3$, CO (60 psig), 70 °C in ACN],[13] indole **2** was produced in high assay yield (95%, Table 1, entry 1). The only by-product was dimer **4** (3%, Fig. 1). Crystallization from the reaction stream resulted in a disappointing isolated yield (45%) due to the presence of triphenylphosphine and triphenylphosphine oxide. Reducing the ligand and catalyst loading resulted in decreased yields due

Table 2. Reductive cyclization using palladium/phenanthroline catalysts[a]

$$\mathbf{3} \xrightarrow[\substack{\text{15 psig CO} \\ \text{solvent, 70 °C}}]{\text{Pd cat, ligand}} \mathbf{2}$$

Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Yield (%)[b]
1	Pd(OAc)$_2$ (1.0)	phen (2.0)	ACN	56
2	Pd(OAc)$_2$ (1.0)	phen (2.0)	THF	37
3	Pd(OAc)$_2$ (1.0)	phen (2.0)	Toluene	40
4	Pd(OAc)$_2$ (1.0)	phen (2.0)	ODCB[c]	58
5	Pd(OAc)$_2$ (1.0)	phen (2.0)	DMF	98 (94)[d]
6	Pd(OAc)$_2$ (0.5)	phen (1.0)	DMF	93
7	Pd(OAc)$_2$ (0.25)	phen (0.5)	DMF	24
8	Pd(OAc)$_2$ (0.10)	phen (0.2)	DMF	0
9	Pd(OAc)$_2$ (0.10)	phen (0.5)	DMF	6
10	Pd(OAc)$_2$ (0.10)	phen (1.0)	DMF	25
11	Pd(OAc)$_2$ (0.10)	tm-phen (0.2)	DMF	25
12	Pd(OAc)$_2$ (0.10)	tm-phen (0.5)	DMF	79
13	Pd(OAc)$_2$ (0.10)	tm-phen (1.0)	DMF	92
14	phen$_2$Pd(BF$_4$)$_2$[e] (1.0)	—	DMF	99
15	phen$_2$Pd(BF$_4$)$_2$ (0.5)	—	DMF	89
16	phen$_2$Pd(BF$_4$)$_2$ (0.25)	—	DMF	74
17	Pd(TFA)$_2$ (0.1)	phen (0.5)	DMF	32
18	Pd(TFA)$_2$ (0.1)	phen (1.0)	DMF	33
19	Pd(TFA)$_2$ (0.1)	tm-phen (0.2)	DMF	68
20	Pd(TFA)$_2$ (0.1)	tm-phen (0.5)	DMF	78
21	Pd(TFA)$_2$ (0.1)	tm-phen (1.0)	DMF	100

[a] Reactions performed at 70 °C and 15 psig CO.

[b] HPLC assay yield.

[c] *ortho*-Dichlorobenzene.

[d] Number in parentheses is yield reported for material isolated by crystallization.

[e] Pre-formed catalyst.