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Note

Aerobic palladium(II) catalysed oxidative route for synthesis of Papaveraldine

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In this paper, an alternate chromatography free route employing aerobic Palladium(II) catalysed base mediated oxidative conditions for synthesis of medicinally promising alkaloid Papaveraldine is reported.

Keywords: Papaveraldine, Palladium acetate, Oxidation, Aerobic, Alkaloid, Synthesis

Alkaloids are studied for past several centuries for their medicinal values in various ancient traditional therapeutic practices. Papaveraldine **1** (Fig. 1) as isolated from *Papaver setigerum* is also tested for its medicinal properties like AChE inhibitory activity[1-5].

The classical synthetic methods known for decades employing oxidation sequence are inefficient due to low yields[6-17]. Several oxidative routes with different starting substrates are explored particularly employing Ir photocatalyst[7], I_2 (Ref. 8), electrochemical[9], $CuBr_2$ (Ref. 10), Fe complex[11], $FeCl_2.4H_2O$ (Ref. 12) N-chlorosuccinimide[14], $PhI(OCOCF_3)_2$ (Ref. 15) and many more[18-22]. Recently, in the course of compilation of this work, a similar route was developed by Toyota *et al*. involving $Pd(OAc)_2$ catalysed tandem oxidation of C-C, C-H, C-N bonds in O_2 atmosphere with overall 61% yield[23]. In this work, we describe the aerobic condition with $Pd(OAc)_2$ in presence of Cs_2CO_3 giving 78% yield of desired alkaloid.

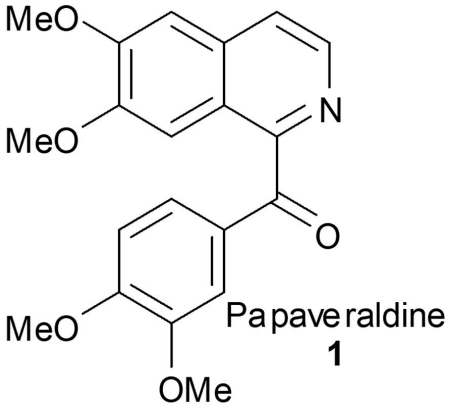
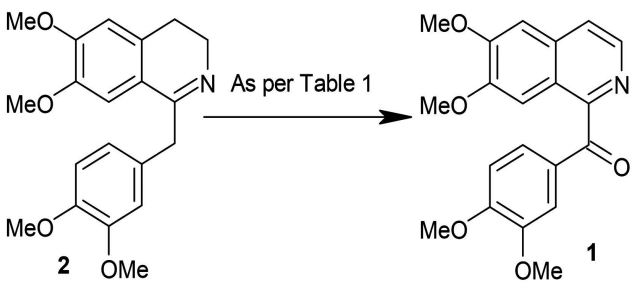


Fig. 1 — Papaveraldine alkaloid

Results and Discussion

In our quest for synthesis of novel heterocyclic systems, dihydroisoquinoline **2** that was prepared for synthesis of pyrroloisoquinoline-2,3-dione as reported in our earlier report[24], this dihydroisoquinoline **2** was further studied for preparation of papaveraldine. Our initial trial for oxidation using $Pd(OAc)_2$ and Cs_2CO_3 in various solvents yielded us desired papaveraldine **1** in 32% isolated yield (Scheme 1). The spectral data for the obtained product was in accordance with the literature data[2,7-11,14]. Method was optimised by changing the molar rati o of catalyst, base, solvent and reaction condition as summarised in Table 1. Maximum yield was obtained using $Pd(OAc)_2$ (20 mol%) and Cs_2CO_3, (100 mol%) in DMSO under aerobic heating condition. Reducing the quantity of catalyst or base drastically affected the yield of desired product. Replacing to milder base did not provide us any encouragement. The role of $Pd(OAc)_2$ and Cs_2CO_3 was also testified as in their absence no appreciable yield was obtained rendering maximum quantity of unreacted dihydroisoquinoline **2**. Other heterogenous catalysts such as ZnO and MgO did not provide us any relief in yield.

Based on this investigation, the transition metal catalyst with base in oxidative solvent and air under reflux conditions proceeded with benzylic oxidation sequential mechanism giving desired natural product **1** in good yield (Scheme 2).

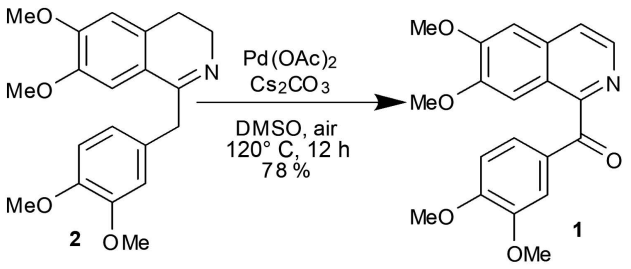


Scheme 1 — Optimisation studies

Table 1 — Optimisation studies as per Scheme 1

Entry	Catalyst	Base	Solvent/ reaction conditions	Isolated Yield (%)
1	$Pd(OAc)_2$	Cs_2CO_3	Toluene, reflux	32
2	$Pd(OAc)_2$	Cs_2CO_3	Dioxane, reflux	40
3	$Pd(OAc)_2$	Cs_2CO_3	DMSO, 120°C	78
4	$Pd(OAc)_2$	Cs_2CO_3, (50 mol%)	DMSO, 120°C	35
5	$Pd(OAc)_2$	–	DMSO, 120°C	28
6	$Pd(OAc)_2$	Na_2CO_3	DMSO, 120°C	59
7	$Pd(OAc)_2$ (10 mol%)	Cs_2CO_3	DMSO, 120°C	58
8	–	Cs_2CO_3	DMSO, 120°C	<10
9	–	–	DMSO, 120°C	<10
10	ZnO	Cs_2CO_3	DMSO, 120°C	22
11	MgO	Cs_2CO_3	DMSO, 120°C	20
12	$Pd(OAc)_2$ (10 mol%) $Cu(OAc)_2$ (20 mol%)	–	Toluene, 120°C, 24 h, O_2 (1 atm)	61 (Ref. 23)
13	–	$NaHCO_3$	DMF, 120°C, 3h, O_2 balloon	57 (Ref. 2)

Reaction conditions: Dihydroisoquinoline **2** (0.5 mmol) Catalyst (0.1 mmol), base (0.5 mmol) solvent (5 mL), 120°C, air, 12 h.



Scheme 2 — Oxidative route for papaveraldine **1**

Experimental Section

In a round bottom flask, Dihydroisoquinoline **2** (0.5 mmol) $Pd(OAc)_2$ (20 mol%) and Cs_2CO_3, (0.5 mmol) were mixed in DMSO (5 mL), and heated at 120°C, in air, for 12 h. Further ice cold water (25 mL) was added and product was extracted in EtOAc (2×20 mL). Combined fractions were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. Analytically pure product was obtained by recrystallisation with EtOAc: Hexanes (1:3).

Light brown solid. m.p.204-206°C (Ref. 2,14). IR (KBr): 3329, 2965, 2835, 1713, 1674, 1535, 1269, 1028 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.87 (s, 6H), 3.97 (s, 3H), 6.76 (d, J = 8.4 Hz, 1H), 7.07 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.57 (d, J = 5.2 Hz, 1H), 7.62 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 54.99 (CH_3), 55.06 (CH_3), 55.11 (2×CH_3), 103.03 (CH), 103.84 (CH), 108.92 (CH), 110.82 (CH), 120.30 (CH), 121.80 (Cq), 125.96 (CH), 128.85 (Cq), 132.98 (Cq), 138.93 (CH), 148.02 (Cq), 150.02 (Cq), 152.22 (Cq), 152.70 (Cq), 152.84 (Cq), 192.98 (Cq); LC-MS: *m/z* $[M+H]^+$ 354.1.

Conclusion

In conclusion, an aerobic Palladium(II) catalysed base mediated oxidative route is developed for synthesis of medicinally important alkaloid papaveraldine.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary Information

Supplementary information is available in the website https://nopr.niscpr.res.in/handle/123456789/58776.

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