Synthesis of isoindolinones *via* carbonylative cyclisation of 2-(2-bromophenyl)-2-oxazolines by a bimetallic palladium–nickel catalyst system

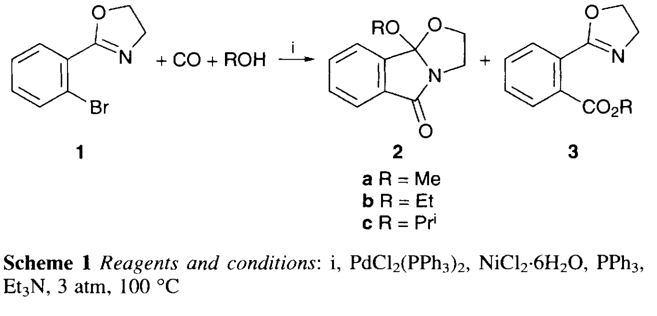
Chan Sik Cho, Jae Wook Lee, Dong Yub Lee, Sang Chul Shim* and Tae Jeong Kim

Department of Industrial Chemistry, College of Engineering, Kyungpook National University, Taegu 702-701, Korea

2-(2-Bromophenyl)-2-oxazolines react with carbon monoxide (3 atm) in alcohol in the presence of a catalytic amount of a bimetallic palladium–nickel catalyst to give the corresponding isoindolinones in high yields.

Transition metal-catalysed carbonylative heterocyclisation has been a useful synthetic tool for the formation of a variety of heterocyclic compounds such as lactams, lactones and imides.[1] As part of our series of studies on the synthesis of heterocyclic compounds catalysed by transition metals, we found recently that 2-bromobenzaldehyde reacted with CO in alcohols in the presence of a catalytic amount of palladium salts to give 3-alkoxy phthalides *via* intramolecular carbonylative cyclisation.[2] The key step of this cyclisation process was the coordination of the oxygen of the formyl group adjacent to the palladium of the aroylpalladium intermediate followed by nucleophilic attack by alcohol. Thus, consideration of this pathway led us to attempt the carbonylative cyclisation of 2-(2-bromophenyl)-2-oxazolines since the oxazoline bears a similar spatial arrangement of molecular structure and coordination function to transition metals as 2-bromobenzaldehyde. Here we report that 2-(2-bromophenyl)-2-oxazolines react with CO in alcohol in the presence of a bimetallic palladium–nickel catalyst to afford the corresponding isoindolinones.

Treatment of 2-(2-bromophenyl)-2-oxazoline **1** with CO (3 atm.) in ethanol in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride (2 mol%) together with triphenylphosphine (8 mol%) and triethylamine (1.3 equiv.) at 100 °C for 24 h afforded the carbonylative cyclised product, isoindolinone **2b** and 2-(2-ethoxycarbonylphenyl)-2-oxazoline **3b** in 53% yield (**2b**:**3b** = 85:15) (Scheme 1). However, the addition of nickel(II) chloride (0.5 mol%) to the system under the same reaction conditions accelerated the reaction, the yield of the products being increased without loss of selectivity with a shorter reaction time (99% yield, **2b**:**3b** = 88:12). In contrast to these results, when only a catalytic amount of the nickel catalyst was used in the reaction, the carbonylative cyclisation scarcely proceeded and the starting oxazoline was recovered. Thus, the co-existence of palladium and nickel catalysts was shown to be necessary for the effective formation of the isoindolinone **2b**. Moreover, the ratio of palladium to nickel has a considerable effect on the yield of **2b** since the use of the molar ratio 0.25 in the reaction afforded, even after a long reaction time, a lower yield of **2b**.



Scheme 1 *Reagents and conditions*: i, $PdCl_2(PPh_3)_2$, $NiCl_2{\cdot}6H_2O$, PPh_3, Et_3N, 3 atm, 100 °C

Among the bases examined, triethylamine was the most effective for the formation of **2b**. The reaction also proceeded using other palladium salts such as $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(MeCN)_2$, $Pd(dba)_2$ and $Pd(PPh_3)_4$ in place of $PdCl_2(PPh_3)_2$ together with $NiCl_2{\cdot}6H_2O$, but the yield of **2b** was generally lower than that when $PdCl_2(PPh_3)_2$ was used together with $NiCl_2{\cdot}6H_2O$ (25–70% yield). Furthermore, the reaction also proceeded using other nickel salts in place of $NiCl_2{\cdot}6H_2O$ together with $PdCl_2(PPh_3)_2$. $NiCl_2(PPh_3)_2$ and $NiCl_2(DPPE)$ exhibited nearly the same catalytic activity as $NiCl_2{\cdot}6H_2O$ under the employed reaction conditions. Typical results are summarised in Table 1.

The carbonylative cyclisation also proceeded in other alcohols such as methanol and isopropanol and with other easily available 2-(2-bromophenyl)-2-oxazolines (Table 2). However, the reaction with the oxazolines containing substituents in the oxazoline ring (**4**–**6**) did not afford satisfactory yields of the isoindolinones under the above optimized reaction conditions. The reaction of oxazolines **4**–**6** requires two or three times the

Table 1 Carbonylative cyclisation of **1** under various conditions[a]

Catalyst			Yield (%)[b]	
Palladium (mol%)	Nickel (mol%)	*t*/h	**2b**	**3b**
$PdCl_2(PPh_3)_2$ (2)	—	24	44	8
$PdCl_2(PPh_3)_2$ (2)	$NiCl_2{\cdot}6H_2O$ (0.5)	12	87	12
$PdCl_2(PPh_3)_2$ (2)	$NiCl_2{\cdot}6H_2O$ (0.5)	6	58	9
—	$NiCl_2{\cdot}6H_2O$ (2)	24	trace	0
$PdCl_2(PPh_3)_2$ (0.5)	$NiCl_2{\cdot}6H_2O$ (2)	24	55	9
$PdCl_2(MeCN)_2$ (2)	$NiCl_2{\cdot}6H_2O$ (0.5)	24	70	8
$PdCl_2$ (2)	$NiCl_2{\cdot}6H_2O$ (0.5)	24	67	8
$Pd(OAc)_2$ (2)	$NiCl_2{\cdot}6H_2O$ (0.5)	24	42	7
$PdCl_2(PPh_3)_2$ (2)	$NiCl_2(PPh_3)_2$ (0.5)	24	91	8
$PdCl_2(PPh_3)_2$ (2)	$NiCl_2(DPPE)$ (0.5)	24	88	9

[a] All reactions were carried out with **1** (1 mmol), PPh_3 (8 mol%) and Et_3N (1.3 mmol) in ethanol (15 ml) at 100 °C under CO (3 atm). [b] Determined by GLC.

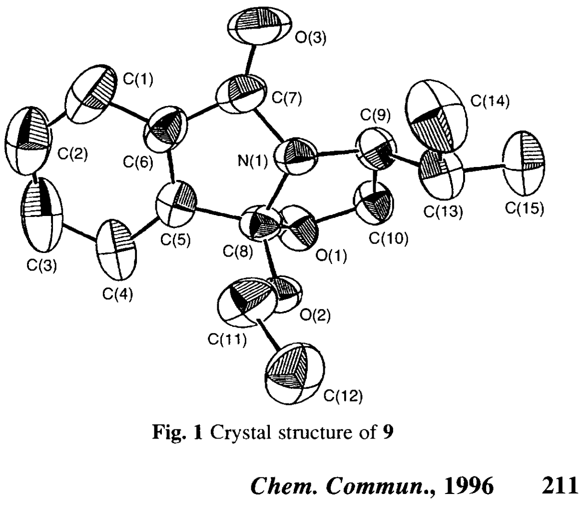
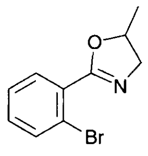
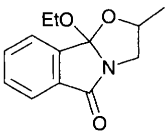
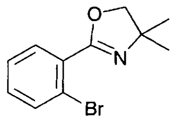
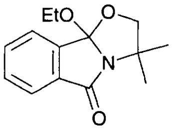
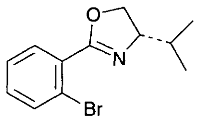
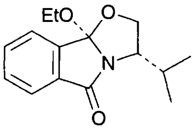
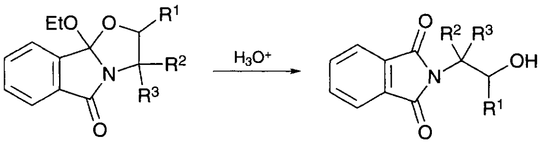


Fig. 1 Crystal structure of **9**

Table 2 Carbonylative cyclisation with various oxazolines[a]

Oxazoline	Alcohol	Catalyst Pd[b] (mol%)	 Ni[c] (mol%)	*t*/h	Product	Isolated yield (%)[d]
1	MeOH	2	0.5	12	**2a**	77
1	EtOH	2	0.5	12	**2b**	80
1	Pr^iOH	4	1	24	**2c**	64
 **4**	EtOH	4	1	24	 **7**	83[e]
 **5**	EtOH	6	1.5	36	 **8**	81
 **6**	EtOH	4	1	24	 **9**	87

[a] All reactions were carried out with oxazoline (1 mmol), PPh_3 (8 mol%), and Et_3N (1.3 mmol) in alcohol (15 ml) at 100 °C under CO (3 atm). [b] $PdCl_2(PPh_3)_2$. [c] $NiCl_2(DPPE)$. [d] In all cases 2-(2-alkoxycarbonylphenyl)-2-oxazolines (< 15%) were also formed. [e] Diastereoisomeric mixture.



10a $R^1 = R^2 = R^3 = H$ 98%
b $R^1 = Me, R^2 = R^3 = H$ 92%
c $R^1 = H, R^2 = R^3 = Me$ 97%
d $R^1 = R^2 = H, R^3 = CHMe_2$ 96%

Scheme 2

amount of catalyst and a longer reaction time to give desirable yields of the isoindolinones **7–9**. In the case of (*S*)-2-(2-bromophenyl)-4-isopropyl-2-oxazoline **6**, the reaction proceeded diastereoselectively to afford the isoindolinone **9**. Detailed structural information of **9** was obtained by X-ray crystal structure determination.† The ORTEP view of **9** (Fig. 1) confirms the (*S*,*R*)-configuration. The isoindolinones thus obtained could be converted to the corresponding phthalimides **10** quantitatively in acidic media (Scheme 2).

This research was supported in part by KOSEF-OCRC and in part by Ministry of Education (BSRI-96-3408). The authors are grateful to the KOSEF for postdoctoral fellowship (C.S.C.) and to Dr Nam Ho Heo and Mr Woo Taik Lim for helpful discussions of X-ray analysis and data.

Footnote

† *Crystal data* for **9**: $C_{15}H_{19}NO_3$, M = 261.324, orthorhombic, a = 8.321(1), b = 8.427(1), c = 20.177(3) Å, V = 1414.8(3) Å^3 (by least-squares analysis of 25 reflections), T = 294 K, space group $P2_12_12_1$ (no. 19), graphite monochromated Mo-Kα radiation, λ = 0.71073 Å, Z = 4, D_c = 1.227 g cm^{-3}, $F(000)$ = 560, a chunky crystal with dimensions 0.32 × 0.32 × 0.32 mm, μ(Mo-Kα) = 0.8 cm^{-1}, semi-empirical absorption correction based on ψ scans, transmission factors 95.9–99.9%; Enraf-Nonius CAD4 diffractometer; 1695 reflections measured, 1217 unique reflections with $I > 3\sigma(I)$ were used during subsequent structure refinement. The structure was solved by direct methods (MULTAN)[3] and subsequent Fourier difference techniques, and refined anisotropically, by full-matrix least-squares, on F^2 (program MolEN).[4] Hydrogen atoms were not included. The weighting scheme was $w^{-1} = \sigma F^2 + (PWT * F)^2 + QWT$ (Killean and Lawrence method).[5] The most suitable values of PWT and QWT for this data were 0.02 and 1.0, respectively. The final discrepancy indices $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = (\Sigma w||F_o| - |F_c||^2/\Sigma w|F_o|^2)^{1/2}$ are 0.069 and 0.086, g.o.f. = 1.67.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/197.

References

1 For reviews see: H. M. Colquhoun, D. J. Thompson and M. V. Twigg, *Carbonylation: Direct Synthesis of Carbonyl Compounds*, Plenum Press, New York, 1991; M. Iwasaki, Y. Ishii and M. Hidai, *J. Synth. Org. Chem., Jpn.*, 1991, **49**, 909; C. Thebtaranonth and Y. Thebtaranonth, *Cyclization Reaction*, CRC Press, London, 1994.

2 S. C. Shim, D. Y. Lee, L. H. Jiang, T. J. Kim and S.-D. Cho, *J. Heterocycl. Chem.*, 1995, **32**, 363.

3 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declerg and M. M. Woolfson, MULTAN 80, University of York, 1980.

4 MolEN, An Interactive Structure Solution Procedure, Enraf-Nonius, Delft, The Netherlands, 1990.

5 R. C. G. Killean and J. L. Lawrence, *Acta Crystallogr., Sect. B*, 1969, **25**, 1750 (PWT and QWT are user defined values, depending on the intensity of the data. The factor PWT adjusts the weighting of large *F*, while the factor QWT has more effect on small *F*).

Received, 20th May 1996; Com. 6/03505A