Pergamon

Tetrahedron Letters 39 (1998) 2421–2424

TETRAHEDRON LETTERS

Preparation of Indole-2-Carboxamides by Palladium-catalysed Carbonylation

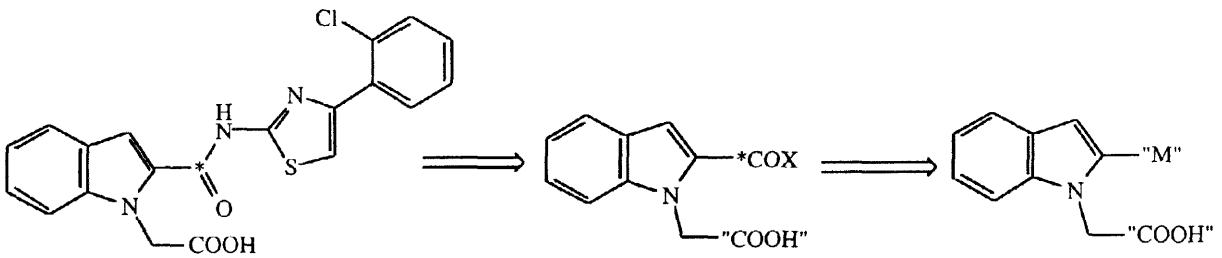
John M. Herbert* and Alan H. McNeill

Isotope Chemistry Laboratories, Department of Preclinical Metabolism and Pharmacokinetics, Sanofi Research, Willowburn Ave., Alnwick, Northumberland NE66 2JH, UK

Received 2 December 1997; revised 19 January 1998; accepted 23 January 1998

Abstract: Palladium-mediated carbonylation of a 2-iodoindole in the presence of an amine provides an efficient method for the preparation of indole-2-carboxamides. The process is clean and rapid, and appears to be general where the amine component is sufficiently non-volatile.

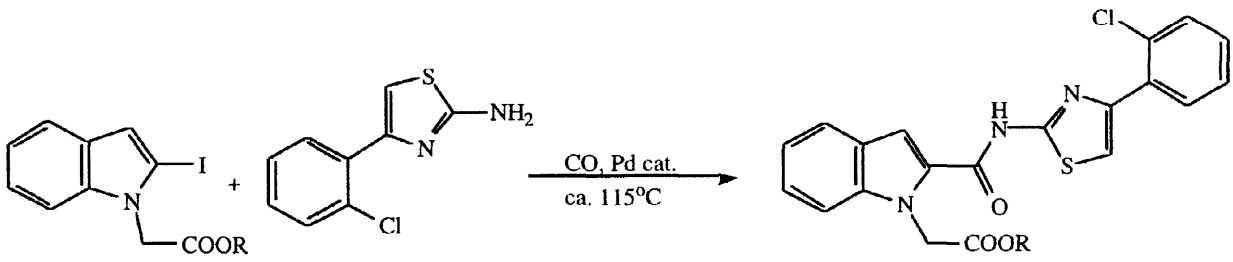
Where electrophilic substitution cannot be directed to C-2 of an indole by blocking C-3, selectivity is commonly obtained by using a substituent at nitrogen to direct metalation at C-2.[1] In general, such processes are not usable if an electrophilic or acidic group is present in the molecule, as in the CCK-A antagonist, *Lintitript* (SR27897, **1**).[2] The present work resulted from the need to develop an approach suitable for application to ^{11}C-labelling of **1**, the labelled carbon being inserted as late as possible in the sequence, in the presence of the carboxylic acid functionality or a derivative (Scheme 1). We chose to investigate a palladium-mediated process for introduction of the carbonyl group at C-2.[3] The formation of amides by carbonylation of amines in the presence of a carbon electrophile is well precedented,[4] and palladium-catalysed carbonylation has been applied recently by Andersson and Langstrom[5] to the introduction of an ^{11}C-labelled carbonyl group into ketones. However, carbonylation of a 2-haloindole appears to be unprecedented, although palladium-mediated substitution of 2-haloindoles using a stannane or a boronic acid as the nucleophile has been reported.[6]



(1)

Scheme 1. Conceptual Approach to **1**.

0040-4039/98/$19.00
PII: S0040-4039(98)00215-9



1 (R = H). **2** (R = t-Bu)

Table 1. Formation of **1** and **2** by Palladium-catalysed Carbonylation

R	*Catalyst (5%)*	*Solvent*	*Yield, %*
t-Bu	$Pd(PPh_3)_4$+ 10%PPh_3	DMSO	27.6
t-Bu	$PdCl_2(PPh_3)_2$	DMSO	24.4
t-Bu	$PdCl_2(PPh_3)_2$	DMA	16
t-Bu	$PdCl_2(PPh_3)_2$ + Bu_3N	DMA	33
H	$Pd(PPh_3)_4$	DMF	8.6

R	*Catalyst (5%)*	*Solvent*	*Yield, %*
H	$Pd(PPh_3)_4$ + 20%PPh3	DMSO	6.0
H	$Pd(PPh_3)_4$	DMA	41
H	$PdCl_2(PPh_3)_2$ - CuI, Bu_3N	DMA	31
H	$PdCl_2(PPh_3)_2$	DMA	76
H	$PdCl_2(PPh_3)_2$ + Bu_3N	DMA	85

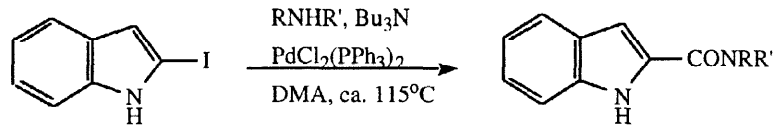
The precursors for the carbonylation reaction, 2-iodoindole-1-acetic acid and its *tert*-butyl ester,[7] were obtained readily by alkylation of the sodium salt of 2-iodoindole[8] with ethyl or *tert*-butyl bromoacetate in DMSO followed, in the former case, by base hydrolysis. Carbonylation of either of these iodoindoles in the presence of 4-(2-chlorophenyl)thiazole and a suitable palladium catalyst was rapid; using the optimised conditions outlined below, carbonylation was normally complete within 5 minutes and in no case was it advantageous to continue the introduction of carbon monoxide for more than 10 minutes.

The efficiency of carbonylation was dependent not only upon the catalyst used, but also upon the reaction solvent: the best combination tested was bis(triphenylphosphine)palladium(II) chloride in *N,N*-dimethylacetamide (DMA). The effect of other common additives was examined also; although the best results were obtained in the presence of tributylamine, its presence was not critical, while addition of copper(I) iodide appeared to inhibit the reaction. A 1:2 ratio of palladium to triphenylphosphine appears to be adequate: yields dropped when more than this quantity of phosphine was used. No attempt was made to carry out the reaction in the absence of triphenylphosphine. In all cases, the reaction proceeded to give a single product: where the yield was poor, the balance was found to consist of starting materials. Thus, the method provided a rapid and effective preparation of **1**. In addition, the *tert*-butyl ester **2**, was cleaved by trifluoroacetic acid in dichloromethane to give **1** in 80% yield.

Having optimised the carbonylation procedure for the preparation of **1**, it was of interest to examine its applicability to a range of amine substrates, the results of which are summarised in Table 2. The yields obtained for the formation of amides **3-6** are essentially as would be expected; it is likely that the poor yield of **8** merely reflects the lesser reactivity of the amine. The modest yield of **5** is disappointing, given the tolerance of acidic functionality already demonstrated in the preparation of **1**, and is presumably a result of the zwitterionic character of glycine. The failure of the known compound **11**[9] to be formed is likely to be a result of physical factors: *N,O*-dimethylhydroxylamine, generated *in situ* from its salt, is likely to evaporate rapidly under the reaction conditions,

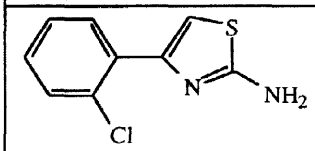
being therefore unavailable to react. An attempt to couple 2-iodoindole with *trans*-4-aminocyclohexanol afforded, unexpectedly, a complex mixture which did not appear to contain either the desired amide or the alternate ester product (these were prepared independently for comparison).

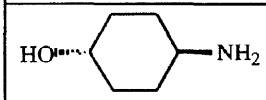
In summary, we have demonstrated the efficiency of palladium-catalysed carbonylation of a 2-iodoindole in the presence of an amine as a means to introduce an amide sidechain at C-2 of an indole. As long as it is carried out at atmospheric pressure, the process is limited principally by the boiling point of the amine, accomodating primary and secondary aliphatic and aromatic amines, and tolerating acidic functionality elsewhere in the molecule.



3-7

Table 2. Formation of Indoles **3-7** by Palladium-catalysed Carbonylation

RNHR'	Product	Yield
	**3**	82%*
$BuNH_2$	**4**	82%
H_2NCH_2COOH	**5**	51%
BnNHMe	**6**	90.5%
$PhNH_2$	**7**	76%

RNHR'	Product	Yield
	-	0
p-$H_2NC_6H_4COCH_3$	**8**	33%
PhNHMe	**9**	97%
$BnONH_2$	**10**	84%
MeONHMe	**11**	0

*11% without Bu3N

The procedure is represented by the preparation of **1**: A solution of 2-iodoindole-1-acetic acid (91 mg, 0.3 mmol), 4-(2-chlorophenyl)thiazol-2-amine[2] (64 mg, 0.3 mmol) and bis(diphenylphosphino)palladium dichloride (10 mg, 0.015 mmol) in anhydrous *N,N*-dimethylacetamide (2.5 ml), under a blanket of nitrogen, was heated in an oil bath at 112-113°C. Carbon monoxide gas was introduced in a slow stream, during 10 minutes, through a fine needle placed below the surface of the solution The mixture was cooled and partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The aqueous phase (containing unreacted 2-iodoindole-1-acetic acid and a little product) was re-extracted with ethyl acetate and the combined organic phases were washed twice with 1N aqueous sodium hydroxide. These extracts (containing slightly impure product) were combined (pH >14) and acidified to approximately pH 1-3 with 1N hydrochloric acid, and extracted with ethyl acetate. The latter extracts were washed once with aqueous sodium hydrogencarbonate, dried ($MgSO_4$), and concentrated under reduced pressure to give **1** (105 mg, 85%) which was recrystallised from ethanol to give white crystals, m.p. 250-252°C (dec.). δ_H (CD_3SOCD_3) 5.58 (s, 2H), 7.15 (ddd, 1H), 7.29 (d, 1H), 7.34 (ddd, 1H), 7.38 (ddd, 1H), 7.44 (ddd, 1H), 7.55 , (ddd, 1H), 7.59 (ddd, 1H), 7.63 (dd, 1H), 7.71 (dd, 1H), 7.84 (ddd, 1H). *m/z* 411, 413 (3:1, $M^{+\cdot}$), 393, 395 (3:1), 237, 239 (3:1), 210, 212 (3:1).

Previously unreported indole-2-carboxamides prepared were:

2: oil, δ_H ($CDCl_3$) 1.45 (s, 9H), 5.29 (s, 2H), 7.12 (ddd, 1H), 7.16 (d, 1H), 7.15-7.50 (m, 7H), 7.64 (dd, 1H), 7.78 (dd, 1H); *m/z* (CI-NH_3) 468.1154 (MH^+; calc. for $C_{24}H_{23}ClN_3O_3S$ 468.1149), 202 (100%).

3: white solid, m.p. 248°C. Found: C, 61.3; H, 3.6; N, 11.7; S, 9.9%. $C_8H_{12}ClN_3OS$ requires C, 61.1; H, 3.4; N, 11.9; S, 10.0%. δ_H(CD_3SOCD_3) 7.08 (ddd, 1H), 7.26 (ddd, 1H), 7.38 (ddd, 1H), 7.45 (ddd, 1H), 7.48 (dd, 1H), 7.57 (dd, 1H), 7.67 (s, 1H), 7.69 (m, 2H), 7.91 (dd, 1H). *m/z* 353.0388, 355 (3:1, $M^{+\cdot}$, calc. for $C_{18}H_{12}ClN_3OS$ 353.0390), 144 (100%).

8: white solid, m.p. 242-244°C. Found: C, 71.2; H, 5.4; N, 9.4 %. $C_7H_{14}N_2O_2.1/2H_2O$ requires C, 71.1; H, 5.3; N, 9.7%. δ_H (CD_3SOCD_3) 2.56 (s, 3H), 7.08 (dd, 1H), 7.24 (dd, 1H), 7.45 (d, 1H), 7.49 (s, 1H), 7.70 (d, 1H), 8.0 (4H), 10.51 (s, 1H). *m/z* 278 ($M^{+\cdot}$, 100%).

6: white solid, m.p. 181-181.5°C. Found: C, 77.1; H, 6.2; N, 10.5%. $C_{17}H_{16}N_2O$ requires C, 77.2; H, 6.1; N, 10.6%. δ_H (CD_3SOCD_3) 3.23 (br s, 3H), 4.80 (br s, 2H), 6.80 (1H, br s), 7.03 (dd, 1H), 7.18 (dd, 1H), 7.25-7.5 (m, 7H), 7.57 (d, 1H). *m/z* 264 ($M^{+\cdot}$), 120 (100%).

10: white solid, m.p. 148-149°C. Found: C, 72.3; H, 5.4; N, 10.2%. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%. δ_H (CD_3SOCD_3) 4.97 (s, 2H), 7.00 (s, 1H), 7.04 (d, 1H), 7.19 (d, 1H), 7.3-7.55 (8H), 7.61 (d, 1H). *m/z* (CI-NH_3) 284 (MNH_4^+), 267 (MH^+, 100%).

References and Footnotes:

1. e.g. Katritzky, A.R., and Akutagawa, K., *Tetrahedron Lett.*, **1985,** *26,* 5935; Edwards, M.P., Doherty, A.M., Ley, S.V., and Organ, H.M., *Tetrahedron,* **1986**, *42,* 3723; Sakamoto, T., Kondo, Y., Takazawa, N., and Yamanaka, H., *J. Chem. Soc., Perkin 1,* **1996**, 1927; Kondo, Y., Yoshida, A., and Sakamoto, T., *J. Chem. Soc., Perkin 1,* **1996**, 2331.
2. Bras, J.P., Frehel, D., Gully, D., and Valette, G., Eur. Pat. Appl. EP432040
3. By comparison, treatment of indole-1-acetic acid with butyllithium followed by *tert*-butyllithium resulted in deprotonation α- to the acid. Attempts to form ortho esters of indole-1-acetic acid were unsuccessful.
4. e.g. Colquhoun, H.M., Thompson, D.J., and Twigg, M.V., Carbonylation: direct synthesis of carbonyl compounds (Plenum, 1991), Chapter 8.
5. Andersson, Y., and Langstrom, B., *J. Chem. Soc., Perkin 1,* **1995**, 287.
6. Joseph, B., Malapel, B., and Mérour, J-Y., *Synth. Commun.,* **1996**, *26,* 3289; Chiu, L., Fisher, M.H., Goulet, M.T., and Wyvratt, M.J., *Tetrahedron Lett.,* **1997**, *38,* 3871..
7. Data for these intermediates are as follows.
   2-Iodoindole-1-acetic Acid: white solid, m.p. 131-136°C. δ_H (CD_3OD) 2.96 (s, 2H), 6.78 (d, 1H), 7.02 (ddd, 1H), 7.10 (ddd, 1H), 7.30 (dd, 1H), 7.47 (ddd, 1H). *m/z* (APCI-) 300 ([M-H]$^-$, 100%).
   tert-Butyl 2-Iodoindole-1-acetate: foam. δ_H ($CDCl_3$) 1.45 (s, 9H), 4.81 (s, 2H), 6.83 (d, 1H), 7.05-7.35 (m, 3H), 7.53 (dd, 1H). *m/z* (CI^+) 358.0301 (100%; $[MH]^+$; calc. for $C_{14}H_{17}INO_2$ 358.0304), 301, 256, 232, 130.
8. Bergman, J., and Venemalm, L., *J. Org. Chem.,* **1992**, *57,* 2495.
9. Dekhane, M., and Todd, R.H., *Tetrahedron,* **1994**, *50,* 6299.

The authors wish to thank Dr. S.J. Byard for NMR data, Dr. T. Dransfield (Department of Chemistry, University of York, U.K.) for high resolution mass spectra, and C.H.N. Analysis Ltd. (Leicester, U.K.) for elemental analysis.