Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7269–7271

TETRAHEDRON LETTERS

Synthesis of 2-acylindole-3-acetic acids: a novel base-mediated indole synthesis

Kazunari Nakao, Yoshinori Murata, Hiroki Koike, Chikara Uchida, Kiyoshi Kawamura, Sachiko Mihara, Shigeo Hayashi and Rodney W. Stevens*

Discovery Chemistry Research, Nagoya Laboratories, Global Research & Development, Pfizer Inc., 5-2 Taketoyo, Aichi 470-2393, Japan

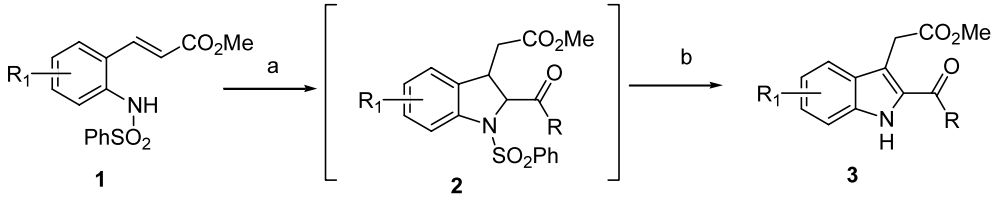
Received 13 June 2003; revised 25 July 2003; accepted 4 August 2003

Abstract—An efficient and expedient synthetic route to 2-acylindole-3-acetic acids is described. This work first demonstrates a one-pot room-temperature indole ring construction via the in situ generation of indoline intermediate.

The chemistry of indoles is well-studied, and a variety of methods for the synthesis of indoles have been developed.[1–3] One of the most important methods for the preparation of many structurally diverse 2,3-disubstituted indoles is the Fisher indole synthesis.[4,5] Recently, a number of novel synthetic methods to indole-3-acetic acid derivatives have been reported on.[6–8] On the other hand, several convenient synthetic methods to 2-acylondoles have been reported. Jones et al. reported a method of the preparation of 2-acylindole derivatives using *N*-alkylation followed by intramolecular aldol condensation and dehydration.[9] His group also reported the similar method to prepare indole-2-carboxilic acids from sulfonamide derivatives.[10] However, 2-acylindole-3-acetic acids have scarcely been reported on because of the low feasibility of the chemistry. Fukuyama et al. have reported on a tin(IV)-mediated synthesis of methyl 2-substituted-indole-3-acetate, however our attempts to couple the intermediate 2-stannylindole with α-halo-ketones under Stille conditions proceeded in unacceptable yields.[11] Herein, we describe an efficient and expedient synthetic route to 2-acylindole-3-acetic acids. This new discovery offers the advantage of a facile one-pot room-temperature indole construction via the in situ generation of indoline intermediate.

Thus, for example, treatment of *trans*-2-aminocinnamate **1** with K_2CO_3 promotes an intramolecular Michael addition that generates indoline **2** and a trace amount of indole **3** (Scheme 1).[12] Subsequent treatment with a base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or Cs_2CO_3, accelerates β-elimination to afford indole **3**.[13] Conveniently, the reaction can be performed in a one-pot procedure to afford the desired indole **3** in a good to excellent yield.

Next, the scope and limitations of the reaction were investigated and results are summarized in Table 1. Electron-donating or -withdrawing group possessing phenacyl (entries 2–7) or heteroarylacyl halides (entries 8–13) all reacted smoothly in situ to provide the corresponding 2-acyl indole acetic esters (52–93% isolated yield). The reaction of 2-bromo-1-cyclopropylethanone



1 2 3

Scheme 1. *Reaction conditions*: (a) $RCOCH_2Br$, K_2CO_3, acetone, rt; (b) base.

* Corresponding author.

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01879-3

Table 1. Methyl 2-acylindole-3-acetate derivatives produced via Scheme 1

Entry	Substrate R_1	Acyl halide	Base (equiv.)	Yield (%)
1	H	$PhCOCH_2Br$	DBU (3)	93
2	6-Cl	4-Cl-$PhCOCH_2Br$	Cs_2CO_3 (2)	61[b]
3	6-Cl	4-Cl-$PhCOCH_2Br$	DBU (2)	52[b]
4	5-Cl	4-Cl-$PhCOCH_2Br$	DBU (3)	88
5	6-MeO	4-Cl-$PhCOCH_2Br$	DBU (3)	74
6	5-MeO	4-Cl-$PhCOCH_2Br$	Cs_2CO_3 (2)	93
7	6-Cl	4-MeO-$PhCOCH_2Br$	Cs_2CO_3 (3)	89
8	5-Cl	5-Cl-2-($BrCH_2CO$)-pyridine	DBU (2)	72[b]
9	5-Cl	4-MeO-2-($BrCH_2CO$)-pyridine*	DBU (2)	74
10	5-Cl	5-Me-2-($BrCH_2CO$)-thiazole[a]	DBU (3)	44
11	5-Cl	1-Me-2-($BrCH_2CO$)-imidazole[a]	DBU (2)	57
12	6-Cl	3-($BrCH_2CO$)-isoquinoline[a]	DBU (3)	53
13	5-Cl	3-($BrCH_2CO$)-isoquinoline[a]	DBU (3)	59
14	6-Cl	Cyclopropyl-$COCH_2Br$	DBU (3)	94
15	6-Cl	1-Bromo-2-butanone	DBU (3)	82

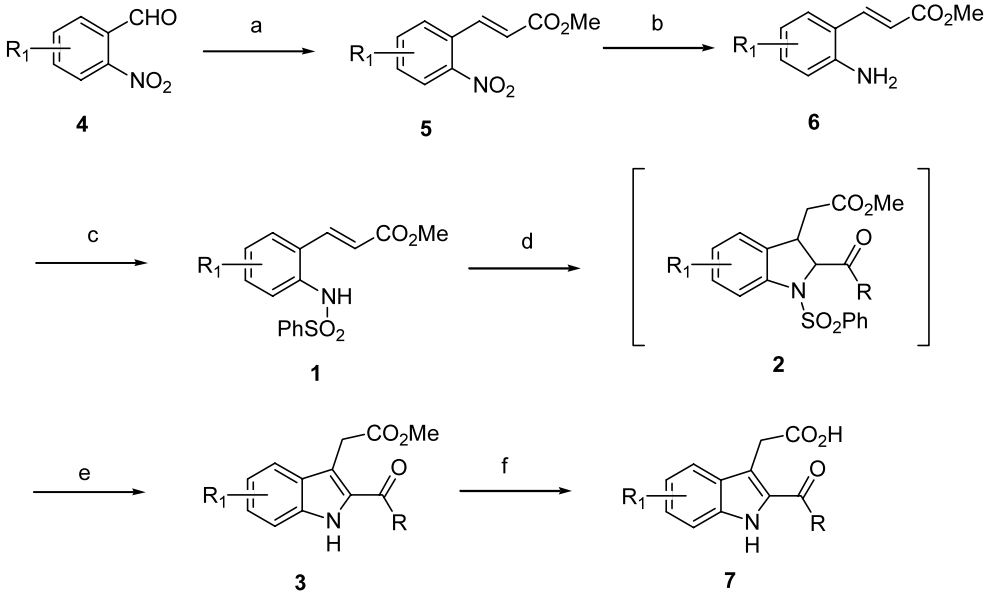
[a] Hydrobromide salt.
[b] Yield after recrystallization.

and 1-bromo-2-butanone also proceeded smoothly to afford the corresponding indole in excellent yield (entries 14 and 15).

trans-2-Aminocinnamates **1** and the title compounds were prepared as follows: Initially we carried out the Wittig reaction of the benzaldehyde **4** to give *trans*-2-nitrocinnamate **5** (Scheme 2) according to the procedure of Carling.[14] *trans*-2-Nitrocinnamate **5** was reduced to *trans*-2-aminocinnamate **6** by treatment with iron powder in refluxing aqueous ethanol and then converted to the acyclic precursor **1** by sulfonylation of **6**. As described above, one-pot room-temperature based-promoted cyclization afforded indole **3** which was hydrolyzed to the corresponding indole acetic acid **7** in excellent yield.

A typical experimental procedure for preparing **3**: A mixture of **1** (1.6 mmol), α-halo-ketone (2.4 mmol) and K_2CO_3 (16 mmol) in acetone (16 mL) was stirred at ambient temperature. After stirring for 1 h, DBU (4.8 mmol) was added and the stirring was continued for an additional 8 h. The mixture was concentrated and the residue was diluted in ethyl acetate (100 mL). The organic mixture was washed with water (100 mL) and dried ($MgSO_4$). After removal of solvent, the residual solids were purified by silica gel column chromatography to afford the corresponding indole **3**.

In summary, this work has first demonstrated a one-pot room-temperature indole construction via the in situ generation of indoline intermediates. This procedure provides a simple and practical method for the synthesis of 2-acylindole-3-acetic acids.



Scheme 2. *Reaction conditions*: (a) $Ph_3P{=}CHCO_2Me$, toluene, reflux; (b) Fe, NH_4Cl, $EtOH/H_2O$, reflux; (c) $PhSO_2Cl$, pyridine, CH_2Cl_2, rt; (d) $RCOCH_2Br$, K_2CO_3, acetone, rt; (e) DBU or Cs_2CO_3; (f) 2N NaOH, THF/MeOH, rt.

References

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
2. Sundberg, R. J. *Indoles*; Academic Press: New York, 1996.
3. Ahamd, A.; Dundar, L. J.; Green, I. G.; Harvey, I. W.; Shepherd, T.; Smith, D. M.; Wong, R. K. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, *19*, 2751–2758.
4. Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245.
5. Robinson, B. *The Fischer Indole Synthesis*; Wiley: New York, 1982.
6. Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. *Synthesis* **2000**, 429–434.
7. Revial, G.; Jabin, I.; Lim, S.; Pfau, M. *J. Org. Chem.* **2002**, *67*, 2252–2256.
8. Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251–10263.
9. Jones, C. D.; Suarez, T. *J. Org. Chem.* **1972**, *37*, 3622–3623.
10. Jones, C. D. *J. Org. Chem.* **1972**, *37*, 3624–3625.
11. Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127–3128.
12. Noe, C. R.; Knollmueller, M.; Schoedl, C.; Berger, M. L. *Sci. Pharm.* **1996**, *64*, 577–590.
13. Boger, D. L.; Brotherton, C. E.; Panek, J. S.; Yphannes, D. *J. Org. Chem.* **1984**, *49*, 4056–4058.
14. Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397–3408.