Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4749-4752, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01028-9

Palladium-Catalyzed Acylation of a 1,2-Disubstituted 3-Indolylzinc Chloride

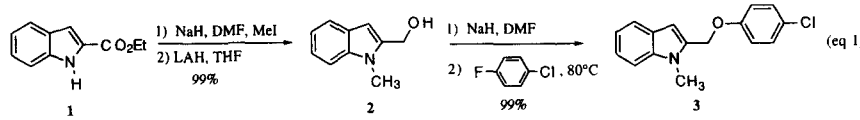
Margaret M. Faul* and Leonard L. Winneroski

Lilly Research Laboratories, A Division of Eli Lilly and Company,
Chemical Process Research and Development Division, Indianapolis, IN 46285

Abstract: 3-Acylindoles were prepared by palladium catalyzed coupling of an acid sensitive 1,2-disubstituted 3-indolylzinc chloride with a number of acid chlorides to give the corresponding ketones in 33-74% yields. © 1997 Elsevier Science Ltd.

A great number of synthetic routes are available to prepare 3-acylindoles.[1] Vilsmeier acylation,[2] Friedel-Crafts acylation,[3] acylation of indole Grignard reagent[4] and acylation of 3-indolylzinc chloride[5] have all been utilized. Despite the seeming generality of these procedures, none are effective for acylation of acid sensitive 2-aryloxyl methyl indoles such as **3**. Palladium catalyzed cross-coupling approaches have been utilized to prepare a wide variety of 2- and 3-substituted indoles, but no methods for the palladium catalyzed acylation of a highly functionalized 3-indolylzinc chloride have been reported. Herein, we wish to report the first example of the palladium catalyzed acylation of a substituted 3-indolylzinc chloride.

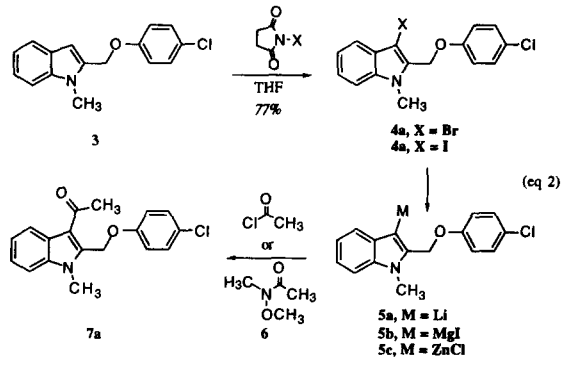
Indole **3** was prepared in three steps: 1) alkylation of the sodium salt of ethyl indole-2-carboxylate with methyl iodide in DMF, 2) LAH reduction of the ester to alcohol **2**, and 3) nucleophilic aromatic substitution of 1-chloro-4-fluorobenzene with the sodium alkoxide of **2** in DMF at 80 °C to give **3** in 98% overall yield (eq 1).



1 2 3

Reaction of **3** with either $POCl_3$/dimethyl acetamide or PPA/acetic anhydride[6] afforded no C-3 acylation, but led to the formation of multiple by-products including *p*-chlorophenol. The acid instability imposed by the 2-aryloxy functionality of **3** dictated the use of basic or neutral acylation conditions.

Preparation of 3-lithioindole **5a** was accomplished by halogen-metal exchange of 3-bromoindole **4a**[7] with either *n*-BuLi or *t*-BuLi at -78 °C (eq 2).[8] However, reaction of **5a** with freshly distilled acetyl chloride at -78 °C produced only small amounts of acylation product **7a** (<4%) and the recovery of mostly hydrogen quenched product **3** (eq 2). Similarly, reaction of acetyl chloride with the Grignard reagent **5b**, prepared from 3-iodoindole **4b**,[9] gave no acylation product and mostly **3**. Reaction of the organolithium **5a** with the Weinreb amide **6** afforded a 43% yield of **7a**.[10]



We next turned our attention to the more stable but less reactive 3-indolylzinc chloride **5c**. Compound **5c** was prepared from 3-bromoindole **4a** by sequential treatment with 2 equiv of *t*-BuLi at -78 °C followed by 1 equiv of $ZnCl_2$ (0.5 molar solution in THF).[11] It has been demonstrated that unsubstituted 3-indolylzinc chloride reacts with acetyl chloride and a variety of other acid chlorides at room temperature without catalysis;[5] however, the 1,2-disubstituted indole **5c** proved to be unreactive towards acetyl chloride under these conditions. Negishi has shown that palladium-phosphine complexes catalyze the reaction of organozincs with acyl chlorides.[12] Previous workers have also shown that 3-indolylzinc halides undergo cross-coupling with aryl and heteroaryl halides in the presence of Pd (0).[13] As an extension to this methodology, we have found that **5c** reacts readily with acetyl chloride at -35 °C in the presence of 10 mole % of a palladium (0) catalyst. The addition of 1 equiv of CuI did not catalyze acylation of **5c**, even after several hours at room temperature.

Optimization of the reactions conditions indicated that 1 equiv of $ZnCl_2$ and 1-3 equiv of acetyl chloride furnished the best yields. Higher equivalents of zinc chloride or acetyl chloride led to lower yields of ketone

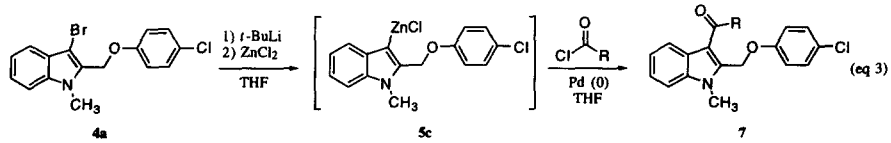


Table. Pd (0) Catalyzed Acylation of 3-Indolylzinc Chloride **5c**

Entry	R	Ketone	Yield[a] (%)
1	CH_3	**7a**	74
2	CH_2Ph	**7b**	61
3	Ph	**7c**	66
4	$(CH_2)_2CH_3$	**7d**	70
5	CH_2Cl	**7e**	33

[a]Yield of analytically pure product.

due to zinc-mediated ring opening of THF with acetyl chloride to generate the corresponding 4-chlorobutyl ester.[14] Under the ideal reaction conditions, ketone **7a** could be prepared in 74% yield (Table, entry 1, eq 3).[15]

To determine the generality of this coupling procedure, **5c** was acylated with a variety of acid chlorides in the presence of Pd (0) to give ketones **7a-d** in 61-70% yield (Table, entries 2-4, eq 3). Low yields (<10%) and poor regioselectivity have been reported on formation of 3-(2-haloacyl)indoles under Friedel-Crafts conditions.[16] Palladium (0) catalyzed coupling of **5c** with chloroacetyl chloride afforded **7e** in 33% yield (Table, entry 5).[17,18]

Preparation of **7a** is representative of the general procedure: To a solution of 1.43 mmol of **4a** in 10 mL of degassed THF at -78 °C was added 2 equiv of 1.7 M *t*-BuLi in pentanes. One equiv of 0.5 M $ZnCl_2$ in THF was added to the reaction after 10 min at -78 °C, and the reaction solution warmed to room temperature and stirred for a total of 1h. The palladium catalyst was prepared *in situ* by treating a suspension of 0.1 equiv of $(PPh_3)_2PdCl_2$ in 5 mL of degassed THF with 0.2 equiv of 2.5 M *n*-BuLi in hexanes.[19] The resultant dark solution was stirred 10 min at room temperature and then 2 equiv of distilled acetyl chloride was added. The catalyst-acid chloride reaction solution was cooled to -35 °C and then the solution of **5c** was added to the reaction mixture keeping the temperature below -30 °C. The reaction was warmed to 0 °C for 2 h, diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine. The product was purified by silica gel chromatography (3/1 hexanes/ethyl acetate) to give 74% of analytically pure **7a**.[20]

Acknowledgments: We would like to thank Dr. Philip Hipskind, Dr. David Mitchell, Thomas Koenig, Nancy Harn, James Nixon and Karen Lobb for helpful discussions during the course of this work.

References and Footnotes

1. (a) Pindur, U.; Pfeuffer, L.; Flo, C. *Chemiker-Zeitung* **1986**, *110*, 307; (b) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York and London, 1970; p. 33; (c) Remers, W. A., *Heterocyclic Compounds, Indole Part 1*, ed. by Houlihan, W. J., John Wiley & Sons, Inc.: New York, 1972; p. 111; (d) *Idem, ibid., Part 3*, 1979; p. 357; (e) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860.
2. Anthony, W. C. *J. Org. Chem.* **1960**, *25*, 2049.
3. Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451.
4. Heacock, R. A.; Kasparek, S. *Adv. Heterocycl. Chem.* **1969**, *10*, 61.
5. Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061.
6. Murakami Y.; Tani, M.; Suzuki, M.; Sudoh, K.; Uesato, M.; Tanaka, K.; Yokoyama Y. *Chem. Pharm. Bull.* **1985**, *33*, 4707.
7. The 3-bromoindole **4a** was prepared as follows: 0.95 equiv of *N*-bromosuccinimide in 100 mL THF was added to a suspension of 37 mmol of **3** in 100 mL of THF over 30 min at -10 °C. The reaction was worked up extractively after 15 min and the product crystallized from 4/1 hexanes/acetone to afford 77% of **4a**.
8. Halogen metal exchange was confirmed by both deuterium quench experiments and reaction of **5a** with methyl iodide.

9. The 3-iodoindole **4b** was prepared as follows: 1.0 equiv of *N*-iodosuccinimide in 25 mL THF was added to a suspension of 11 mmol **3** in 25 mL of THF over 20 min at rt. The reaction was worked up extractively after 30 min and the product purified by flash chromatography using 4/1 hexanes/EtOAc to afford 78% of **4b**.
10. Oster, T. A.; Harris, T. M. *Tetrahedron Lett.* **1983**, *24*, 1851.
11. (a) Amat M.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 793; (b) Erdik, E. *Tetrahedron* **1992**, *48*, 9577; (c) Knochel, P.; Singer R. D. *Chem Rev.* **1993**, *93*, 2117.
12. Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T. *Tetrahedron Lett.* **1983**, *24*, 5181.
13. (a) Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. *Tetrahedron Lett.* **1993**, *34*, 5955; (b) Amat, M.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 793.
14. Bhar, S.; Ranu, B. C. *J. Org. Chem.* **1995**, *60*, 745.
15. The reactions were very selective and compound **3** was the major reaction by-product formed during preparation of **7a-e** under the optimal conditions.
16. (a) Murakami, Y.; Tani, M.; Tanaka, K.; Yokoyama, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2023; (b) Murakami, Y.; Tani, M.; Suzuki, M.; Sudoh, K.; Uesato, M.; Tanaka, K.; Yokoyama, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4707.
17. Higher yields of 3-(2-haloacyl)indoles (49%) have been obtained by reaction of indole with *N*-acylpyridinium salts although preparation of **7e** using these conditions was unsuccessful: Bergman, J.; Backvall, J. E.; Lindstrom, J. O. *Tetrahedron* **1973**, *29*, 971.
18. Reaction of **5a** with 2-chloro-*N*-methoxy-N-methylacetamide afforded **7e** in only a 14% yield.
19. Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338.
20. Compound **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96-7.93 (m, 1H), 7.41-7.29 (m, 3H), 7.22-7.19 (m, 2H), 6.98-6.95 (m, 2H), 5.75 (s, 2H), 3.86 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.14, 156.43, 140.26, 137.21, 129.35, 126.28, 125.49, 123.17, 122.25, 121.15, 116.17, 115.70, 110.04, 60.33, 31.74, 30.58. MS (FD): *m/z* = 313 (M^+, 100%). Anal. calcd for $C_{18}H_{16}NO_2$ Cl: C, 68.90; H, 5.14; N, 4.46; Found: C, 68.77; H, 5.04; N, 4.47.

(*Received in USA* 17 *April* 1997; *accepted* 22 *May* 1997)