A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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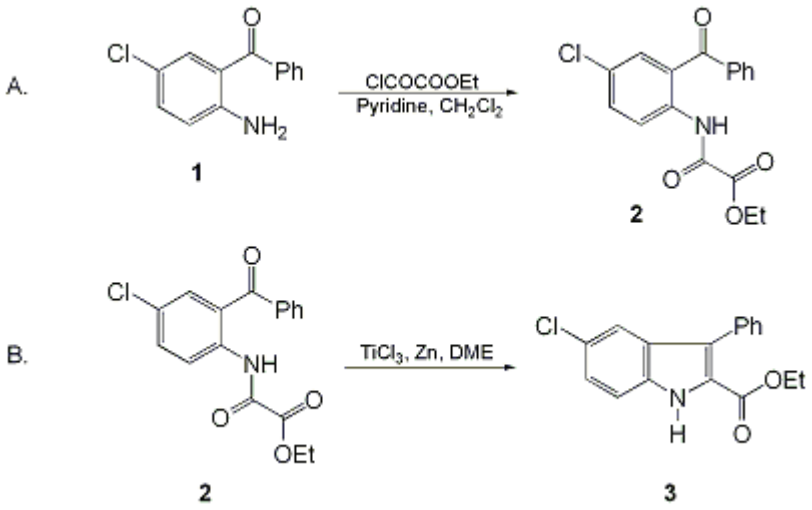
ETHYL 5-CHLORO-3-PHENYLINDOLE-2-CARBOXYLATE

[1H-Indole-2-carboxylic acid, 5-chloro-3-phenyl-, ethyl ester]



Submitted by Alois Fürstner, Achim Hupperts, and Günter Seidel[1] .
Checked by Michael C. Hillier and Stephen F. Martin.

1. Procedure

Ethyl oxalyl chloride is a corrosive lacrymator and the reaction should be carried out in a well-ventilated hood.

A. *N-(2-Benzoyl-4-chlorophenyl)oxalamic acid ethyl ester* . A two-necked, round-bottomed flask (500 mL) equipped with a Teflon-coated magnetic stirring bar, a gas inlet, and a dropping funnel is purged with argon. The flask is charged with 2-amino-5-chlorobenzophenone (13.9 g, 60 mmol, (Note 1)), dichloromethane (100 mL), and pyridine (20 mL , (Note 2)). A solution of ethyl oxalyl chloride (9.6 g, 70.3 mmol, (Note 1)) in dichloromethane (20 mL) is added dropwise through the addition funnel over a period of 45 min at 0°C (ice bath), and the resulting suspension is stirred for another 1.5 hr at ambient temperature. An aqueous saturated solution of sodium bicarbonate (40 mL) is added dropwise, and the biphasic system is stirred for 1.5 hr until evolution of gas ceases. The layers are separated, and the aqueous layer is extracted with dichloromethane (3 × 50 mL). The combined organic phases are washed with water (50 mL), dried (Na_2SO_4), filtered, and evaporated. The residual pyridine is removed by azeotropic distillation with toluene (3 × 100 mL) under reduced pressure on a rotary evaporator, and the residue is dried under vacuum (10^{-3} mm) to afford N-(2-benzoyl-4-chlorophenyl)oxalamic acid ethyl ester (19.6 g, 98%), that is directly used in the next step (Note 3), (Note 4).

B. *Ethyl 5-chloro-3-phenylindole-2-carboxylate* . An oven-dried, two-necked, round-bottomed, 500-mL flask equipped with a Teflon-coated magnetic stirring bar, a glass stopper, and a reflux condenser connected to the argon line is flushed with argon. The flask is charged with N-(2-benzoyl-4-chlorophenyl)oxalamic acid ethyl ester (13.27 g, 40 mmol), titanium(III) chloride ($TiCl_3$) (12.34 g, 80 mmol), zinc dust (10.45 g, 160 mmol, (Note 5)), and ethylene glycol dimethyl ether (DME) (250 mL, (Note 6)). The resulting suspension is heated at reflux for 2 hr with stirring, during which time a characteristic color change from violet ($TiCl_3$) to blue to black occurs (Note 7). The mixture is allowed to cool to ambient temperature and then slowly filtered through a short pad of silica on a sintered glass funnel. The inorganic residues are thoroughly washed with ethyl acetate (5 × 50 mL , (Note 8)), and the combined filtrates are concentrated to dryness on a rotary evaporator. For purification, the crude product is refluxed in toluene (120 mL, (Note 9)), and the resulting yellow solution is decanted from the oily

residues. The product crystallizes upon standing at ambient temperature. The precipitated needles are collected on a funnel, washed with cold hexane (3 × 10 mL), and dried under reduced pressure to afford a first crop of ethyl 5-chloro-3-phenylindole-2-carboxylate as pale-yellow needles (9.3-9.7 g, 78-81%). Evaporation of the filtrate and recrystallization of the residue from toluene (20 mL) as described above gives a second fraction of product (0.8-1.4 g, 7-12%) (Note 10).

2. Notes

1. 2-Amino-5-chlorobenzophenone (98%) and ethyl oxalyl chloride (98%) were purchased from Aldrich Chemical Company, Inc. , and used as received.
2. Dichloromethane (99.6%) was freshly distilled under argon from calcium hydride . Pyridine (99%+) was dried over activated molecular sieves (4 Å) and distilled under reduced pressure prior to use.
3. The crude product is ≥ 98% pure by GC. The checkers used the following conditions for GLC analysis: injector: 250°C, column: 90°C to 300°C, rate; 12°C/min.
4. The product has the following properties: mp 132-134°C (uncorrected), 135.9°C (differential scanning calorimetry, DSC), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (t, 3 H, J = 7.2), 4.42 (q, 2 H, J = 7.2), 7.45-7.76 (m, 7 H), 8.67 (d, 1 H, J = 9.6), 12.04 (br s, 1 H, -NH) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 63.6, 122.8, 125.5, 128.5, 129.0, 129.9, 132.7, 133.0, 133.8, 137.0, 137.4, 155.0, 160.1, 197.6 .
5. $TiCl_3$ (Aldrich Chemical Company, Inc., 99%) and zinc dust (Aldrich Chemical Company, Inc., 98+%, <10 micron) were used as received. A substrate : $TiCl_3$ ratio of 1 : 2 is usually required to ensure quantitative conversions.
6. DME (Merck-Schuchardt, 99%+) was freshly distilled under argon from either sodium-potassium alloy or potassium/benzophenone prior to use.
7. Thorough mixing of the black suspension during reflux was neccessary to obtain optimal yields.
8. Occasionally the mixture must be passed through silica twice to obtain a clear filtrate.
9. Toluene (99%+) was distilled prior to use. Alternatively, the product can be recrystallized from ethyl acetate (50 mL) / hexane (350 mL).
10. The compound has the following properties: pale-yellow crystals, purity: ≥ 98% (GC); mp 169-172° C (uncorrected), 178°C (DSC); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.21 (t, 3 H, J = 7.0), 4.28 (q, 2 H, J = 7.0), 7.34-7.61 (m, 8 H), 12.20 (br s, 1 H, -NH) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.1, 60.7, 114.7, 119.6, 122.1, 124.5, 125.4, 127.3, 128.1, 130.6, 133.2, 134.8, 161.2 .

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Low-valent titanium, formed from $TiCl_x$ (x = 3, 4) and various reducing agents, exhibits a high oxophilicity and a strong reducing ability. This particular combination of properties provides the driving force for the reductive coupling of carbonyl compounds to alkenes. Generally referred to as the "McMurry olefin synthesis",[2,3] two important extensions to this reaction have recently been found:

(1) As far as starting materials are concerned, its scope has been significantly expanded beyond aldehydes and ketones. Thus, a new approach to aromatic heterocycles such as furans, benzo[b]furans, pyrroles, and indoles has been devised, based on the reductive cyclization of oxo-ester- or oxo-amide derivatives,[4,5,6,7,8,9,10,11] although amides have previously been considered inert towards activated titanium. This new method has already found applications in the syntheses of alkaloids as well as of pharmaceutically active target molecules.[7,8,9,10].

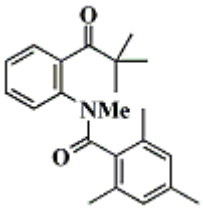
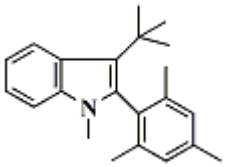
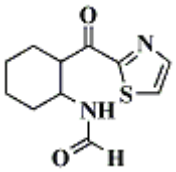
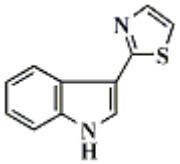
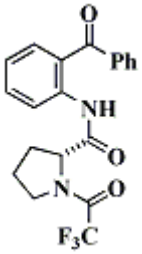
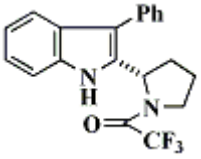
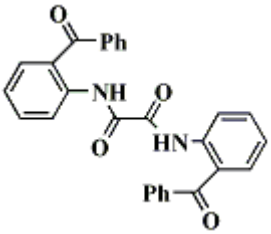
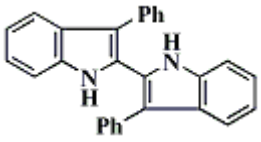
(2) The experimental set-up of titanium-induced reductions has been considerably simplified. McMurry reactions were generally performed in two consecutive steps, consisting of the preparation of the active titanium slurry by reduction of $TiCl_x$ (x = 3, 4) with strong and potentially hazardous reducing agents (e.g., K, Li, Na, C_8K, $LiAlH_4$), followed by the addition of the respective carbonyl compound. The submitters have devised a shorter method, which relies upon the preparation of the active species *in the presence of the substrate* and the use of commercial zinc dust as the reducing agent.[6]

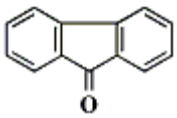
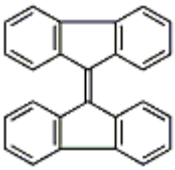
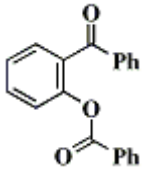
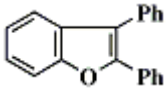
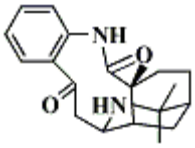
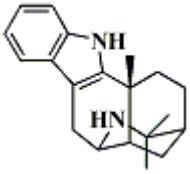
Precoordination of the $TiCl_3$ to the carbonyl group thereby ensures a "site selective" formation of the coupling agent in this one-pot procedure.

The reductive cyclization of substrate **2** to ethyl 5-chloro-3-phenylindole-2-carboxylate, **3**, which is a known precursor for diazepam (Valium),[12] nicely illustrates these advancements. Although compound **2** bears four different reducible groups (amide, aryl chloride, ester, and ketone), the desired indole **3** is formed in a completely chemo- and regioselective way. This strong bias for a low-valent, titanium-promoted oxo-amide coupling is quite representative and renders the method compatible with an array of different functional groups including acetals, alkenes, alkyl chlorides, (remote) amides, aryl halides, (remote) esters, ethers, nitriles, cyclopropyl-, furanyl-, pyridyl-, thiazolyl-, trifluoromethyl-, and N-tosyl groups. Even free carboxylic acids and unprotected, remote ketone groups may be resistant to the reaction conditions.[5,6,7,8,9,10,11]

This one-pot procedure for titanium-induced reactions is also applicable to the synthesis of crowded products,[6] to completely chemo- and regioselective "zipper-type" polycyclizations,[11] to bimolecular reductions of alkynes,[6] and to conventional McMurry reactions of aldehydes or ketones.[6] Some representative examples are compiled in the Table.

TABLE
REDUCTIVE CYCLIZATIONS WITH LOW-VALENT TITANIUM REAGENTS

Substrate	Product	Yield
		88%
		71% [a]
		90% [b]
		81%

		92%
		76%
		75% [a]

[a]After work-up with aq. EDTA; [b]ee (substrate) = ee (product) = 93%.

References and Notes

1. Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim a. d. Ruhr, Germany.
2. McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513;
3. Fürstner, A.; Bogdanovic', B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2443.
4. Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991.
5. Fürstner, A.; Jumbam, D. N. *J. Chem. Soc., Chem. Commun.* **1993**, 211.
6. Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215.
7. Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, *127* 1125;
8. Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773;
9. Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637;
10. Fürstner, A.; Ernst, A.; Krause, H.; Ptock, A. *Tetrahedron* **1996**, *52*, 7329.
11. Fürstner, A.; Ptock, A.; Weintritt, H.; Goddard, R.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 678.
12. Yamamoto, H.; Inaba, S.; Hirohashi, T.; Ishizumi, K. *Chem. Ber.* **1968**, *101*, 4245.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl 5-chloro-3-phenylindole-2-carboxylate:
Indole-2-carboxylic acid, 5-chloro-3-phenyl-, ethyl ester (8);
1H-Indole-2-carboxylic acid, 5-chloro-3-phenyl-, ethyl ester (9); (21139-32-2)

Ethyl oxalyl chloride:
Glyoxylic acid, chloro-, ethyl ester (8);
Acetic acid, chlorooxo-, ethyl ester (9); (4755-77-5)

N-(2-Benzoyl-4-chlorophenyl)oxalamic acid ethyl ester:

Oxanilic acid, 2'-benzoyl-4'-chloro-, ethyl ester (8);
Acetic acid, [(2-benzoyl-4-chlorophenyl)amino]oxo-, ethyl ester (9); (19144-20-8)

2-Amino-5-chlorobenzophenone:
Benzophenone, 2-amino-5-chloro- (8);
Methanone, (2-amino-5-chlorophenyl)phenyl- (9); (719-59-5)

Pyridine (8,9); (110-86-1)

Titanium(III) chloride (8,9); (7705-07-9)

Zinc (8,9); (7440-66-6)

Ethylene glycol dimethyl ether:
Ethane, 1,2-dimethoxy- (8,9); (110-71-4)