Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3875–3878

A practical synthesis of 3-indolyl α,β-unsaturated carbonyl compounds

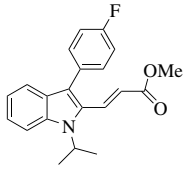
Weiqi Wang and Tetsuya Ikemoto*

Fine Chemicals Research Laboratory, Sumitomo Chemical Co., Ltd, 3-1-21, Utajima, Nishiyodogawa-ku, Osaka 555-0021, Japan

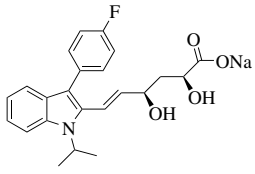
Received 26 January 2005; revised 14 March 2005; accepted 25 March 2005
Available online 13 April 2005

Abstract—An acid-catalyzed practical synthesis of 3-indolyl α,β-unsaturated carbonyl compounds using methyl 3-methoxyacrylate, methyl 3,3-dimethoxypropionate, or 1,1-dimethoxy-3-butanone is reported. 35% HCl aqueous solution catalyzes this reaction efficiently in acetic acid. One of the most favorable substrates is 3-(4-fluorophenyl)-1-isopropyl-1*H*-indole, which reacts nearly quantitatively to give the corresponding α,β-unsaturated ester, and the scope of the reaction can be extended to some electron-rich benzene derivatives.

3-Indolyl α,β-unsaturated carbonyl compounds are very useful agricultural and pharmaceutical intermediates. Compound **1** is an intermediate of fluvastatin **2**, a well-known HMG-CoA reductase inhibitor.[1] Synthesis of these α,β-unsaturated esters usually needs at least two steps. As far as we know, there are two general protocols, one is Vilsmerer formylation followed by condensation of acetate derivatives and the other is halogenation followed by Heck reaction.[2] There were also some examples reported on direct oxidative coupling of arenes in the early 1980s, using acrylates together with stoichiometric palladium acetate.[3] Several examples of catalytic oxidative coupling with olefins using palladium catalyst were also reported; however, they still need stoichiometric organic or inorganic oxidants.[4] Recently, catalytic oxidative coupling reactions using molecular oxygen as the oxidant were reported,[5] while they seem much better from an economical point of view, molecular oxygen is not necessarily industrially favorable from the point of view of safety. As a result of our study aimed to find an economical and practical synthetic method of compound **1**, we have found an effective acid-catalyzed practical synthetic method using methyl 3-methoxyacrylate or methyl 3,3-dimethoxypropionate, which are supplied industrially in large quantities.



1



2

The reaction was initially conducted by mixing methyl 3-methoxyacrylate (2 equiv) with compound **3** (1 equiv) in the presence of $POCl_3$ (2 equiv); however, the product **1** was obtained in poor yield. Next, the effect of water was investigated. Thus, as shown in Table 1, water was found to notably accelerate the reaction. In the case of addition of 2 equiv of H_2O, the yield was 63% in only *E*-form. Methyl 3,3-dimethoxypropionate also provided the corresponding ester in 53% yield. However, from the point of large-scale production, the yields and the conditions were still unsatisfactory.

Acetic acid, which is often used as a solvent of many kinds of electrophilic reactions of indole derivatives, came to our attention. The usability was soon confirmed as shown in Table 2. It was gratifying to note that the product was obtained in high yields. The reaction needs only a catalytic amount of $POCl_3$, unlike in MeCN, which usually needs more than 1 equiv M of $POCl_3$. In

Keywords: 3-Methoxyacrylate; 3,3-Dimethoxypropionate; α,β-Unsaturated carbonyl; Fluvastatin.
* Corresponding author. Tel.: +81 6 64739899; fax: +81 6 64734012; e-mail: ikemotot2@sc.sumitomo-chem.co.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.195

Table 1. $POCl_3$ catalyzed preparation in MeCN[a]

Entry	Reagent (equiv)	Catalyst (equiv)	Water (equiv)	Time (h)	Yield[b] (%)
1	**4** (2)	$POCl_3$ (2)	None	18	32
2	**4** (2)	$POCl_3$ (2)	1	18	46
3	**4** (2)	$POCl_3$ (2)	2	18	63
4	**5** (2)	$POCl_3$ (2)	2	18[c]	53

[a] Compound **3** (1.2 mmol), MeCN (6 mL), 25 °C.
[b] HPLC calculated yield from the peak area against the standard compounds.
[c] Carried out at 50 °C.

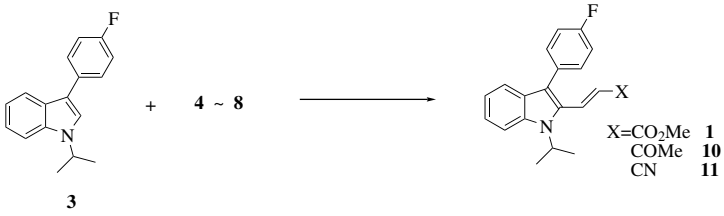
order to find more convenient acidic catalysts, other acids were examined. Nearly all kinds of the protonic acid except H_3PO_4, exhibited catalytic activity, especially a hydrochloride aqueous solution was effective as well as $POCl_3$. The corresponding α,β-unsaturated ketone **10**[8] was also obtained by using 1,1-dimethoxy-3-butanone in 39% yield. The yield was slightly improved when formic acid was used as a solvent. 3-Methoxyacrylonitrile and 3,3-dimethoxypropionitrile also react to provide the corresponding α,β-unsaturated nitrile **11**,[8] however, the yield was not so good even when formic acid was used as the solvent.

In order to examine the role of water in the reaction, the corresponding reactions with or without water were carried out as shown in Table 3. These results show that water is certainly necessary in the case of using methyl 3-methoxyacrylate, while it is unnecessary in the case of using methyl 3,3-dimethoxypropionate. That means that this reaction is neither via a direct Michael type 1,4-addition to 3-methoxyacrylate nor via a simple Friedel–Crafts type reaction to oxocarbenium ions **4b**, but possibly via an S_N2 type nucleophilic substitution mechanism to the protonated hemiacetal **4a** or protonated acetal **5a** by electron-rich aromatic compounds, as

Table 2. Acid catalyzed preparation in AcOH[a]

Entry	Reagent (equiv)	Catalyst (mol %)	Water (equiv)	Time (h)	Yield[b] (%)
1	**4** (2)	$POCl_3$ (20)	1	9	79
2	**4** (2)	$POCl_3$ (40)	1	9	95[c]
3	**4** (2)	$BF_3{\cdot}Et_2O$ (65)	1	15	17
4	**4** (2)	H_3PO_4 (65)	1	15	0
5	**4** (2)	H_2SO_4 (65)	1	15	59
6	**4** (2)	HCl (65)	2.5[d]	15	94[c]
7	**4** (2)	HBr (65)	3.3[e]	5	90[c]
8	**6** (2)	HCl (65)	2.5[d]	18	39[f]
9	**6** (2)	HCl (65)	2.5[d]	18	50[f,g]
10	**7** (2)	$POCl_3$ (50)	1	15	36[h]
11	**8** (2)	HCl (5)	2.5[d]	18	25[h]
12	**8** (2)	HCl (65)	2.5[d]	18	20[g,h]

[a] Compound **3** (2.45 mmol), AcOH (6 mL), 25 °C.
[b] HPLC calculated yield from the peak area against the standard compounds.
[c] Isolated yield.
[d] 35% HCl aqueous solution was used.
[e] 48% HBr aqueous solution was used.
[f] Product: (*E*)-4-[3-(4-fluoro-phenyl)-1-isopropyl-1*H*-indol-2-yl]-but-3-en-2-one **10**.
[g] Formic acid (6 mL) was used instead of AcOH.
[h] Product: (*E*)-3-[3-(4-fluoro-phenyl)-1-isopropyl-1*H*-indol-2-yl]-acrylonitrile **11**.



(1)

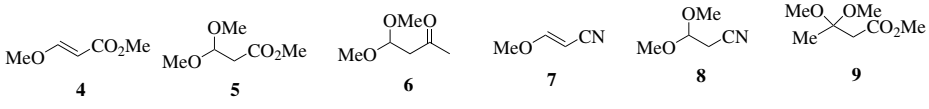


Table 3. The role of water[a]

Entry	Reagent (equiv)	Catalyst (mol %)	Water	Time (h)	Yield[b] (%)
1	**4** (2)	HBr[c] (65)	None	5	13
2	**4** (2)	HBr[c,d] (65)	None	5	5
3	**5** (2)	HBr[c] (65)	None	5	90
4	**5** (2)	HBr[c,d] (65)	None	5	95

[a] Compound **3** (2.45 mmol), AcOH (6 mL), 25 °C.
[b] HPLC calculated yield from the peak area against the standard compounds.
[c] Anhydrous 30% HBr/AcOH was used.
[d] Ac_2O (0.2 equiv) was added to the reaction mixture in order to strictly suppress the influence of water.

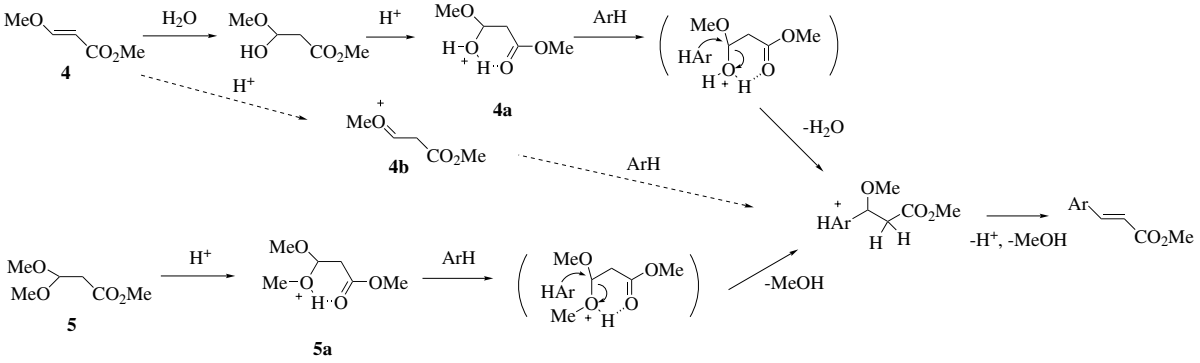
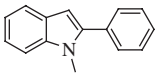
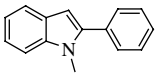
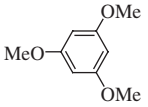
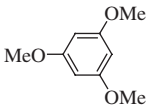
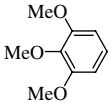


Figure 1. Proposed reaction mechanism.

Table 4. Substrates other than compound **1**[a]

Entry	Substrate	Reagent	Catalyst (mol %)	Water (equiv)	Time (h)	Yield[b] (%)
1		**4**	$POCl_3$ (5)	1	7	82[c]
2		**6**	35% HClaq (30)	—	14	89[d]
3		**4**	$POCl_3$ (5)	1	7	—[e]
4		**4**	$POCl_3$ (5)	1	7	—[e]
5		**4**	$POCl_3$ (5)	1	5	92[f]
6		**4**	35% HClaq (30)	—	1	98[f]
7		**4**	$POCl_3$ (5)	1	18	25[g]

[a] Substrate (5 mmol), reagent (5.5 mmol), AcOH (6 mL), 25 °C.
[b] Isolated yield.
[c] Product: (*E*)-3-(1-methyl-2-phenyl-1*H*-indol-3-yl)-acrylic acid methyl ester **12**.
[d] Product: (*E*)-4-(1-methyl-2-phenyl-1*H*-indol-3-yl)-but-3-en-2-one **13**.
[e] Obtained as a complicated mixture.
[f] Product: (*E*)-3-(2,4,6-trimethoxy-phenyl)-acrylic acid methyl ester **14**.
[g] Product: (*E*)-3-(2,3,4-trimethoxy-phenyl)-acrylic acid methyl ester **15**.

shown in Figure 1. The proposed reaction mechanism is also supported by the fact that the ketal **9** does not react at all under the same condition.

Finally, in order to define the scope and limitations of this methodology, some other aromatic substrates were applied as shown in Table 4. 1-Methyl-2-phenyl-1*H*-indole afforded the corresponding α,β-unsaturated ester **12**[8] or α,β-unsaturated ketone **13**[8] in high yield, while 1-methylindole or indole gave complex mixtures. We tried to apply to some other electron-rich hetero-aromatic compounds like 2,3-benzofuran, 2-butylbenzofuran, benzo[*b*]thiophene, 2-methybenzo[*b*]thiophene, 2,5-dimethylpyrrole, and 1,2,5-trimethylpyrrole using methyl 3-methoxyacrylate, however, the corresponding α,β-unsaturated esters were not obtained. On the other hand, some electron-rich benzene derivatives like 1,3,5-trimethoxybenzene or 1,2,3-trimethoxybenzene afforded the corresponding α,β-unsaturated esters **14**[6] or **15**,[7] respectively. Among these, 1,3,5-trimethoxybenzene showed very high reactivity to give the corresponding ester as a sole product, while 1,4-dimethoxybenzene, 1,3-dimethoxybenzene, or anisole did not react at all.

Typical reaction proceeded as follows: To a mixture of 3-(4-fluorophenyl)-1-isopropyl-1*H*-indole **3** (620 mg, 2.45 mmol) and methyl 3-methoxyacrylate (570 mg, 4.91 mmol) in AcOH (6 mL) was added 35% HCl aqueous solution (166 mg, 1.59 mmol) at 25 °C, and the mixture was stirred at room temperature for 15 h. Water (12 mL) was added to the reaction mixture, then the produced crystals were filtered, washed with MeOH/H_2O (4/16 mL), and dried under reduced pressure to give methyl *trans*-3-[3-(4-fluorophenyl)-1-isopropyl-1*H*-indol-2-yl]acrylate **1** (777 mg, 94%).

In summary, we have found an acid-catalyzed practical synthetic method for 3-indolyl α,β-unsaturated carbonyl compounds using methyl 3-methoxyacrylate, methyl 3,3-dimethoxypropionate, or 1,1-dimethoxy-3-butanone. The method can also be applied successfully to some electron-rich benzene derivatives.

Acknowledgements

We appreciate a referee for giving us a valuable suggestion on the mechanism of this reaction.

References and notes

1. (a) Kathawala, F. G. PCT Int Appl. WO 8402131, 1984; (b) Prous, J.; Castañer, J. *Drugs Future* **1991**, *16*, 804–810.
2. (a) Wolleb, A.; Wolleb, H. PCT Int Appl. WO 0192223, 2001; (b) Lednicer, D. In *The Organic Chemistry of Drug Synthesis*; John Wiley: New York, 1995; Vol. 5, pp 105–107.
3. (a) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851–855; (b) Murakami, Y.; Yokoyama, Y.; Aoki, T. *Heterocycle* **1984**, *22*, 1493–1496.
4. (a) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657–2662; (b) Itahara, T.; Kawasaki, K.; Ouseto, F. *Synthesis* **1984**, 236–237; (c) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097–2100; (d) Boele, M. D. K.; Van Strijdonck, G. P. F.; De Vries, A. H. M.; Kamer, P. C. J.; De Vries, J. G.; Van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.
5. (a) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337–338; (b) Yokota, T.; Tani, M.; Sakaguchi, K.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476–1477.
6. Gross, A.; Borcherding, D. R.; Friedrich, D.; Sabol, J. S. *Tetrahedron Lett.* **2001**, *42*, 1631–1633.
7. Peterson, J. R.; Russell, M. E.; Surjasasmita, I. B. *J. Chem. Eng. Data* **1988**, *33*, 534–537.
8. Spectral data for selected compounds: Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (6H, d, J = 7 Hz), 2.23 (3H, s), 4.94 (1H, m), 6.28 (1H, d, J = 16 Hz), 7.09–7.40 (6H, m), 7.51 (1H, d, J = 8 Hz), 7.57 (1H, d, J = 8 Hz), 7.65 (1H, d, J = 16 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 28.2, 48.1, 112.2, 115.6, 115.8, 120.3, 120.5, 120.6, 123.8, 128.3, 128.8, 130.7, 131.7, 131.8, 131.9, 136.8, 160.7, 163.3, 197.3. MS (ESI) *m/e*: 322 $(M+H)^+$. Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (6H, d, J = 7 Hz), 4.85 (1H, m), 5.35 (1H, d, J = 17 Hz), 7.08–7.22 (3H, m), 7.27–7.38 (3H, m), 7.46 (1H, d, J = 8 Hz), 7.48 (1H, d, J = 17 Hz), 7.55 (1H, d, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 48.1, 98.3, 106.4, 112.0, 115.9, 116.1, 118.2, 120.5, 120.6, 124.3, 128.2, 129.4, 129.8, 131.7, 131.8, 136.6, 138.7, 163.3. MS (ESI) *m/e*: 305 $(M+H)^+$. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (3H, s), 3.73 (3H, s), 6.46 (1H, d, J = 16 Hz), 7.30–7.41 (5H, m), 7.50–7.53 (3H, m), 7.72 (1H, d, J = 16 Hz), 7.99 (1H, d, J = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.2, 51.2, 110.0, 110.3, 112.5, 120.6, 121.7, 123.0, 125.5, 128.6, 129.1, 130.0, 130.8, 137.9, 138.8, 145.3, 168.7. MS (ESI) *m/e*: 292 $(M+H)^+$. Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (3H, s), 3.65 (3H, s), 6.83 (1H, d, J = 16 Hz), 7.30–7.43 (5H, m), 7.52–7.59 (4H, m), 8.02 (1H, d, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.1, 31.3, 110.1, 110.4, 120.8, 121.8, 123.0, 123.1, 125.4, 128.6, 129.3, 129.9, 130.8, 137.9, 138.0, 145.9, 198.4. MS (ESI) *m/e*: 276 $(M+H)^+$.