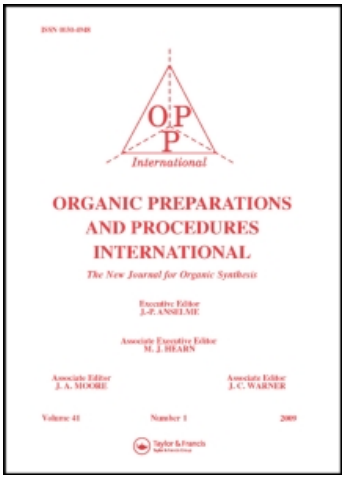

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A Practical Synthesis of (7-Methoxynaphth-1-yl)acetic Acid

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To cite this Article Tang, Jia-Deng and Cen, Jun-Da(2009) 'A Practical Synthesis of (7-Methoxynaphth-1-yl)acetic Acid', Organic Preparations and Procedures International, 41: 2, 164 — 168
To link to this Article: DOI: 10.1080/00304940902802347
URL: http://dx.doi.org/10.1080/00304940902802347

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Organic Preparations and Procedures International, 41:164–168, 2009

ISSN: 0030-4948 print
DOI: 10.1080/00304940902802347

A Practical Synthesis of (7-Methoxynaphth-1-yl)acetic Acid

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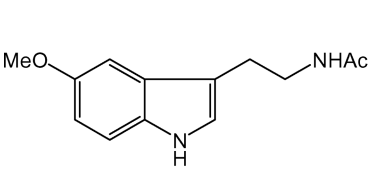
The neurohormone melatonin (5-methoxy-*N*-acetyltryptamine, **1**), which is mainly secreted from the pineal gland or chemically synthesized, is putatively involved in several physiological processes including circadian rhythms, retinal physiology, seasonal breeding, and cardiovascular regulation.[1–3] Since the therapeutic efficacy of melatonin is limited by its short biological half-life, analogs of melatonin were designed and synthesized. It is known that naphthalenic ligands have a high affinity for the melatonin receptor.[4] Among these ligands, *agomelatine* (*N*-[2-(7-methoxynaphth-1-yl) ethyl]acetamide, **2**), which contains the naphthalene moiety instead of indole nucleus, is currently in clinical trial.[5]



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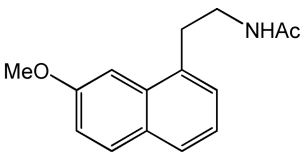

2

(7-Methoxynaphth-1-yl)acetic acid (**6**), a key intermediate to **2**, has been prepared in three steps using substituted tetralone **3** as starting material[6] (*Scheme*). Treatment of **3** with $BrCH_2CO_2Et$ through a Reformatsky reaction afforded **4b** whose extranuclear double bond

Submitted July 14, 2008.
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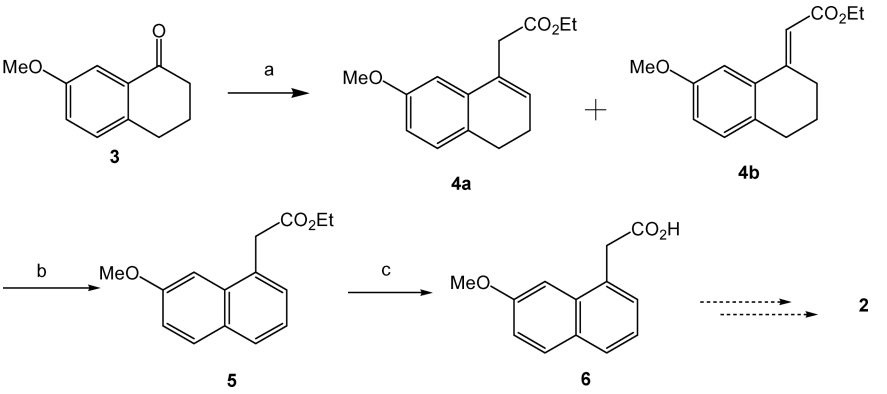
was indicated by the ultraviolet absorption; it was dehydrogenated with sulfur at 215°C to give compound **5** which was hydrolyzed to afford compound **6** in 56% overall yield from **3**.[7] This method suffers from drawbacks such as the use of noxious benzene as solvent and sulfur for dehydrogenation at high temperatures. Actually, the product of this Reformatsky reaction is a mixture of **4a** and **4b** as reported by Ferraz;[7] the isolated yields of **4a** and **4b** were 56% and 13%, respectively (**4a:4b** = 4.3:1). It was speculated that the intranuclear double bond of **4a** tends to make aromatization more facile than for the extranuclear double bond of **4b**. As we expected, when **4a** and **4b** were separated by chromatography and aromatized, **4a** can be dehydrogenated easily with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 at room temperature for 1 hour, whereas **4b** cannot be dehydrogenated with DDQ at reflux in CH_2Cl_2 after 24 hours. Herein, we report a practical synthesis of compound 6 in high yields. The Wittig-Horner reaction is applied in the preparation of compound **4a** and **4b**. Treatment of **3** with diethyl ethoxycarbonylmethanephosphonate in the presence of NaOEt in tetrahydrofuran (THF) under reflux for 12 hours affords a mixture of **4a** and **4b** in 99% yield with **4a:4b** in a ratio of 9.4:1. It is noteworthy that, when ethanol was used as solvent instead of THF under reflux, the reaction was incomplete after 24 hours.



Reformatsky Reaction Conditions:[7]a) $BrCH_2CO_2Et$, Zn, I_2, benzene, 74%; b) sulfur, 215°C 80%; c) 10%NaOH, ethanol, reflux, 94%. Total yield of 6: 56% (based on 3).
Wittig-Horner Reaction Conditions: a) $(EtO)_2P(=O)CH_2CO_2Et$, NaOEt, THF, reflux, 99%, **4a:4b** = 9.4:1; b) DDQ, CH_2Cl_2, 15°C; c) NaOH/EtOH, reflux. Total yield of **6**: 76% (based on **3**).

The product of the Wittig-Horner reaction, in which the intranuclear double bonded **4a** predominates, was subjected directly to the subsequent dehydrogenation with DDQ under mild conditions to afford a high yield of ester **5** which could be hydrolyzed in the next step without purification. Refluxing of **5** in ethanolic sodium hydroxide solution gave, after the removal of solvent, a residue that was dissolved in water and acidified by 10% hydrochloric acid to afford the target compound **6** as a crystalline solid in an overall yield of 76% from **3** compared to 56% for the Reformatsky reaction.

Experimental Section

All melting points are uncorrected. ^{1}H NMR data were recorded on an Inova-400 spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. Mass spectra were performed on Micro Mass Q-Tof Micro MS. Diethyl ethoxycarbonylmethanephosphonate was prepared in 80% yield according to Wu *et al*.[8] as a colorless liquid, bp. 129–131°C/6mmHg (lit.[8] bp.142–145°C/1.2kPa, yield 89%).

Ethyl (7-Methoxy-3,4-dihydronaphthalen-1-yl)acetate (4a) and Ethyl (7-Methoxy-1,2,3, 4-tetrahydro-1-naphthalenylidene)acetate (4b)

Sodium (1.38 g, 60 mmol) was dissolved in dry ethanol (50 ml) and after complete removal of ethanol under reduced pressure, the residual sodium ethoxide was taken up in dry THF (50 ml). Diethyl ethoxycarbonylmethanephosphonate (13.44 g, 60 mmol) was added at room temperature and the mixure stirred for 10 minutes, then 3 (5.28 g, 30 mmol) was added in one portion and the mixture was refluxed for 12 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (150 ml), washed with water (30 ml × 3) and brine (50 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure to provide 10.6 g of a red oil, which was used for the subsequent dehydrogenation without further purification.

Separation and Analysis of 4a and 4b

For identification of **4a** and **4b**, the above crude mixture was chromatographed on silica gel using petroleum ether (bp. 60–90°C)/ethyl acetate (60:1) as eluent, give **4a** (6.6 g, 89%) as a colorless oil, ESI-MS (m/z): 269.00 ([M+Na]). ^{1}H NMR ($CDCl_3$, 400M): δ 1.24 (t, J = 7.4 Hz, 3 H), 2.27–2.32 (m, 2 H), 2.72 (t, J = 8.0 Hz, 2 H), 3.40 (s, 1 H), 3.41 (s, 1 H), 3.78 (s, 3 H), 4.14 (q, J = 7.1 Hz, 2 H), 6.02 (t, J = 4.4 Hz, 1 H), 6.68 (dd, J = 2.8 Hz and 8.0 Hz, 1 H), 6.80 (d, J = 2.4 Hz, 1 H), 7.04 (d, J = 8.0 Hz, 1 H).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.30; H, 7.25.

4b (0.7 g, 9.5%) as a colorless oil, ESI-MS (m/z): 269.03 ([M+Na]). ^{1}H NMR ($CDCl_3$, 400 M): δ 1.32 (t, J = 7.2 Hz, 3 H), 1.84 (t, J = 6.0 Hz, 2 H), 2.73 (t, J = 6.4 Hz, 2 H), 3.15–3.18 (m, 2 H), 3.82 (s, 3 H), 4.21 (q, J = 7.2 Hz, 2 H), 6.29 (s, 1 H), 6.87 (dd, J = 2.4 Hz and 8.4 Hz, 1 H), 7.06 (d, J = 8.8 Hz, 1 H), 7.15 (d, J = 2.4 Hz, 1 H).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.26; H, 7.19.

The overall yield of **4a** and **4b** was 99%.

Ethyl (7-Methoxynaphth-1-yl)acetate (5).
a) Using a Mixture of 4a and 4b as Starting Material

To a solution of 2,3-dichloro-5,6-dicyano-1,4- benzoquinone (DDQ, 8.12 g, 36 mmol) in anhydrous CH_2Cl_2 (100 ml) was added dropwise a solution of the above isolated red oil (10.6 g, about 30 mmol of **4a** and **4b**) in anhydrous CH_2Cl_2 (50 ml) at about 15°C. After addition, the mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered and the precipitate was washed by CH_2Cl_2 (50 ml), the combined organic phase

was washed successively with a saturated $NaHCO_3$ solution (50 ml × 3), water (50 ml) and brine (50 ml), dried over $MgSO_4$. The solvent was removed under reduced pressure to afford crude 5 (9.0 g, 95%) as a red oil, which was used directly in the next step without further purification.

Analytically pure **5** was obtained as a colorless oil by silica gel chromatography using petroleum ether (bp. 60∼90°C)/ethyl acetate (60:1) as eluent. ^{1}H NMR ($CDCl_3$,400 M): δ 1.18 (t, J = 6.8 Hz, 3 H), 3.88 (s, 3 H), 4.08 (s, 2 H), 4.13 (q, J = 6 Hz, 2 H), 7.20 (dd, J = 2.4 Hz and 8.8 Hz, 1 H), 7.27–7.33 (m, 2 H), 7.40 (d, J = 6.8 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.86 (d, J = 9.2 Hz, 1 H).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.60; H, 6.45.

b) Using 4a as Starting Material

To a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.38g, 6.1 mmol) in anhydrous CH_2Cl_2 (20 ml) was added dropwise a solution of **4a** (1.0 g, 4.07 mmol) in anhydrous CH_2Cl_2 (10 ml) at about 15°C. After addition, the mixture was stirred at room temperature for 1 hour. The mixture was filtered and the precipitate was washed by CH_2Cl_2 (10 ml), the combined organic phase was washed successively with saturated a $NaHCO_3$ solution (10 ml × 3), water (10 ml) and brine (10 ml), dried with $MgSO_4$. The solvent was removed under reduced pressure to afford a colorless oil (0.9 g, 91%) which was identified as compound 5 by TLC and ^{1}H NMR.

When **4b** was used instead of **4a** for dehydrogenation with DDQ. Compound **5** was not detected by TLC even after 24 hours.

(7-Methoxynaphth-1-yl)acetic Acid (6)

To a solution of sodium hydroxide (2.95 g, 73.8 mmol) in ethanol (100 ml) was added 9.0 g (about 30 mmol) of crude 5. After reflux for 2 hours, the solvent was removed under reduced pressure and the residue was dissolved in water (50 ml). The aqueous solution was cooled in an ice-water bath and 10% hydrochloric acid was added to pH 1–2. After stirring for 1 hour, the solid was collected, washed four times with water and dried at 70°C to afford 6 as a beige powder (4.9 g, 76% overall yield), mp. 150–152°C(lit.[7] mp. 149.5–150°C). ESI-MS (m/z): 215.24 ([M-H]), ^{1}H NMR ($CDCl_3$, 400 M): δ 3.88 (s, 3 H), 3.99 (s, 2 H), 7.2 (dd,J = 2.4 Hz and 8.8 Hz, 1 H), 7.28–7.32 (m, 2 H), 7.39 (d, J = 6.4 Hz, 1 H), 7.77 (d, J = 8.4 Hz, 1 H), 7.86 (d,J = 8.8 Hz, 1 H).

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.11; H, 5.42.

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Organic Preparations and Procedures International, 41:168–171, 2009

ISSN: 0030-4948 print
DOI: 10.1080/00304940902802370

A Simple and Convenient Synthesis of Triprolidine

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Triprolidine (**3**)[1] is an anti-histamine drug belonging to 1,1-diaryl-2-propyleneamine class[1] having trade names *Actidil*™ and *Myodil*™. It is a very popular first-generation anti-histamine used for coughs and colds. In combination with *pseudo*-ephedrine, it is being sold under the brand name *Actifed*™. Recently Bolser,[2] Pratter, and Abouzgheib[3] reported that for coughs associated with the common cold, first-generation anti-histamine decongestants would be more effective than newer nonsedative antihistamines. This observation together with continuous demand for first-generation anti-histamines prompted us to search for nonhazardous commercially viable alternate synthesis of triprolidine.

The carbon-carbon double bond in propyleneamines such as *Acrivastine*,[4–7] *Pyrrobutamine*,[8,9] *Triprolidine*, *Zimeldine*[10] have been built by dehydration of corresponding alcohols[11–14] or by the Wittig method.[15] *n*-Butyllithium has been employed in both the Wittig condensation and in the preparation of the tertiary alcohol (*Scheme 1*) at around −70°C. However, large-scale preparations of these compounds employ the dehydration method rather than the Wittig method because no efficient method was available for preparation of the intermediates such as 2-(*N,N*-dialkylaminoethyl)triphenylphosphonium bromides and 2-aroylpyridines. Having developed commercially viable methods for the preparation of 2-(p-toloyl)pyridine (**1**)[16] and 2-(*N*-pyrrolidinoethyl)triphenylphosphonium bromide (**2**)[17] we now report the preparation of triprolidine (**3**) without the use of *n*-butyllithium.

The existing industrial scale preparation of triprolidine[11–14] involves the condensation of 2-bromopyridine with β-pyrrolidino-4-methylpropiophenone using alkyllithium at around −70°C followed by dehydration using sulfuric acid between 140

Submitted August 29, 2008.
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