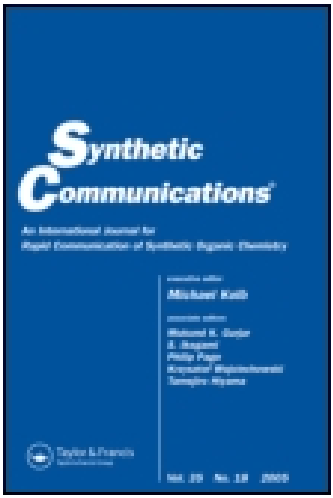

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Efficient Synthesis of 7-Amino-3-hydroxyindan-1-one

Raj (S. B.) Rajur,[1] Venugopal N. Rao,[1] Hwa-Ok Kim,[1] Pamela Nagafuji,[1] Xavier Hearult,[1] John D. Williams,[2] and Norton P. Peet[1,2]

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Abstract: An efficient and reliable three-step synthesis of 7-amino-3-hydroxyindan-1-one (**7**) is described. Compound **7** is a versatile, three-dimensional, three-point scaffold that is useful for the construction of focused compound libraries.

Keywords: HMBC, hydroxyindanones

INTRODUCTION

Fused-ring systems containing a five-membered ring annellated to a six-membered ring provide ideal scaffolds for anchoring multiple functionalities that can engage in specific interactions with biological receptors. These biologically important 5,6-fused systems include indoles (**1**), isatins (**2**), benzofuranones (**3**), indanes (**4**), indanones (**5**), and indenes (**6**), as shown in Fig. 1.

Recent references describe specific examples of these ring systems and their utilities. Indole scaffolds interact with protein-coupled amino acid transporters (PAT1) expressed in several cell types;[1] indoles display melatonin-like cytoprotective activity;[2] and indoles have also been shown to bind the colchicine site of tubulin.[3] Isatin derivatives have been designed to possess antimalarial activity[4] and treat tropical diseases,[5]

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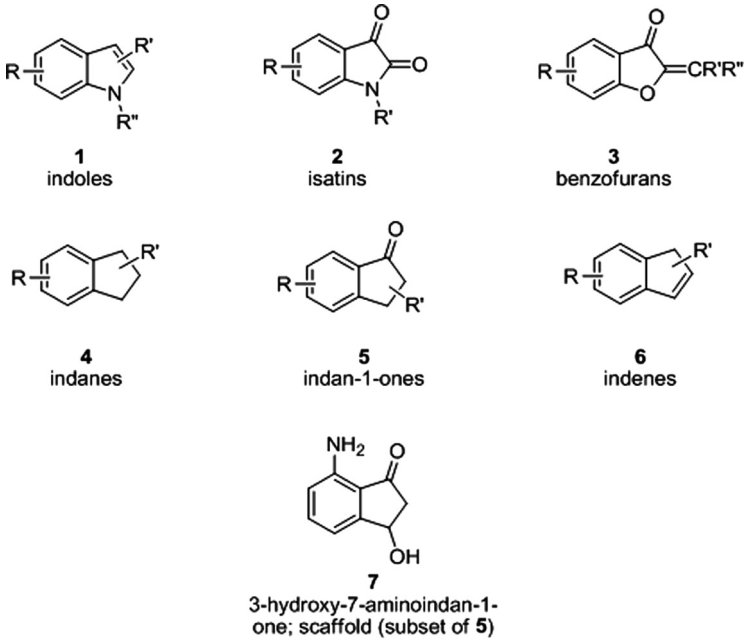


Figure 1. Biologically important 5,6-fused ring systems.

including severe acute respiratory syndrome (SARS) virus[6] and parasitic diseases that are treatable by inhibiting target cysteine proteinases: cruzain, falcipain-2, and rhodesian.[7] Indanes have been used as potassium channel blockers for the treatment of atrial arrhythmias[8] as well as antibacterial agents by the mimicry of a complementary unit on magainin 2.[9] An indene scaffold has been used to make an $\alpha_v\beta_3$ integrin antagonist.[10] Interestingly, indanone derivatives, which are known to possess biological activity,[11] have very recently been synthesized using a triple cascade process: a Knoevenagel condensation followed by a Nazarov cyclization and an electrophilic fluorination.[12] In addition, benzofuranones have recently been reported as flavopiridol mimics.[13]

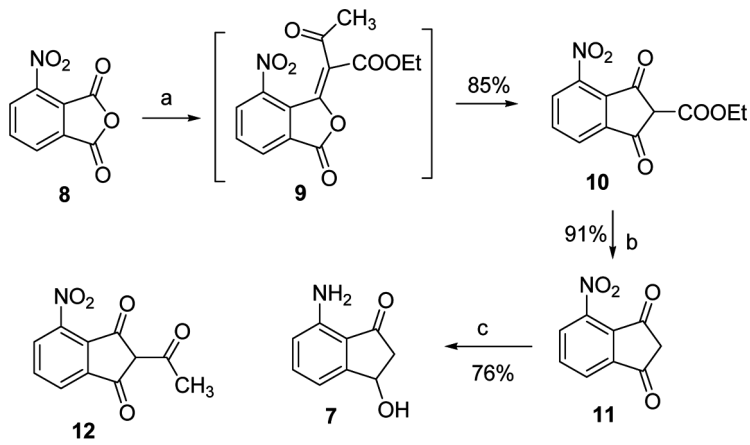
The specific scaffold that is the topic of this report is 7-amino-3-hydroxyindan-1-one (**7**), as shown in Fig. 1. Note that compound **7** is a subset of scaffold **5**.

Although indanone **7** has been mentioned in the literature, its preparation has not been recorded, and the reported synthesis of its precursor is an experimental procedure that we could not repeat as described. In addition to the synthesis of indanone **7**, we describe the preparation of a small set of derivatives that were prepared by functionalization of the amino group.

RESULTS AND DISCUSSION

The preparation of 7-amino-3-hydroxyindan-1-one (**7**) is shown in Scheme 1. A solution of 4-nitrophthalic anhydride (**8**) in methylene chloride was sequentially treated with ethyl acetoacetate, acetic anhydride, and triethylamine. The reaction solution was concentrated, and the residue was reconstituted in water, cooled to 0 °C, and acidified with aqueous hydrochloric acid. The precipitate was collected and dried to give an 85% yield of pure **10**. We were unable to repeat a literature report[14] that lacked details and did not specify any solvent for this reaction. We determined that critical features for this successful conversion were (1) the use of methylene chloride as a solvent; (2) reconstitution of the concentrated reaction mixture in water; and (3) the precipitation of the desired reaction product from the cold aqueous solution. We envision that condensation product **9** is an intermediate in the conversion of **8** to **10**. The synthesis of 2-acetyl-1,3-indanedione (**12**), a compound that is similar to **10**, has also been reported from **8**.[15]

Compound **11** is also reported in the old Russian literature in which they describe a three-step procedure starting from 3-nitrophthalic anhydride and malonic acid.[16] Our melting point (130–132 °C) for **11** is in good agreement with their reported[16] melting point (133 °C). However, we were unable to repeat their reported procedure in spite of several attempts.

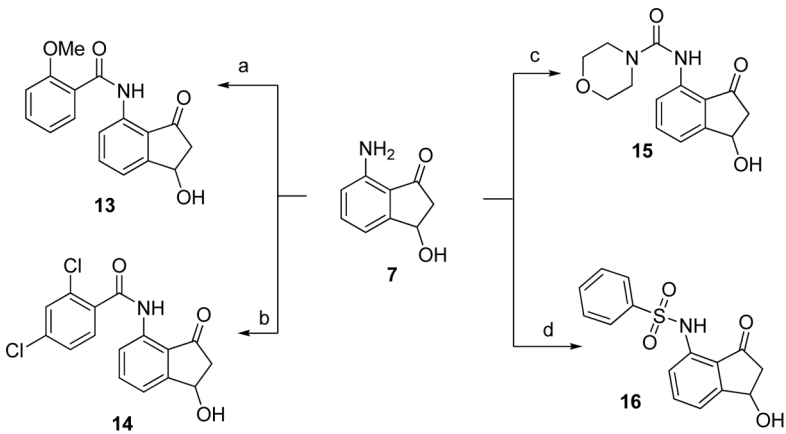


Scheme 1. Reagents and conditions: (a) ethyl acetoacetate, acetic anhydride, triethylamine, dichloromethane, room temperature, 30 min; (b) trifluroacetic, acetonitrile, room temperature, 45 min; (c) 40 psi H_2, 10% Pd/C, methanol, 24 h.

Hydrolysis and decarboxylation of **10** proceeded smoothly with trifluoroacetic acid in acetonitrile to give a 91% yield of 4-nitroindan-1,3-dione (**11**). Simultaneous reduction of the nitro group and the distal carbonyl group of **11** by catalytic hydrogenation gave a 76% yield of the desired three-point scaffold, 7-amino-3-hydroxyindan-1-one (**7**).

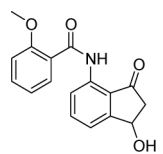
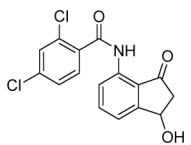
The synthesis of *N*-substituted derivatives of compound **7** were performed using the straightforward derivatization procedures shown in Scheme 2. Treatment of **7** with 2-methoxybenzoyl chloride, 2,4-dichlorobenzoyl chloride, 4-morpholinecarbonyl chloride, and phenylsulfonyl chloride provided good yields of the respective N-substituted compounds **13**–**16**. Physical constants, spectral data, and percentage yields are shown for these derivatives in Table 1.

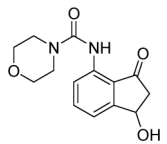
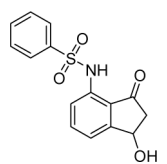
The derivatives of compound **7** shown in Table 1 offered the opportunity to perform diagnostic NMR experiments to unequivocally determine the structure of scaffold **7**. To our knowledge, this determination has not previously been reported. Thus, for compound **13**, as shown in Fig. 2, the two possible structures are as shown for compound **13** and, correspondingly, for the scaffold from which they were derived. The possible structures **A** and **B** (Fig. 2) cannot easily be differentiated by simple ^{1}H or ^{13}C NMR spectroscopy; however, the unusually high shift of the amide –NH (11.92 ppm for this structure vs. 8.5 ppm for *N*-phenyl acetamide) suggested to us that the carbonyl group was proximal to the amide (e.g., structure **A**). This was confirmed by a heteronuclear multiple bond



Scheme 2. Reagents and conditions: (a) 2-methoxbenzoyl chloride, DIEA, DCE, room temperature; (b) 2,4-dichlorobenzoyl chloride, DIEA, DCE, room temperature; (c) 4-morpholinecarbonyl chloride, DIEA, DCE, room temperature; (d) phenylsulfonyl chloride, DIEA, DCE, room temperature.

Table 1. Small library of *N*-substituted derivatives of scaffold **7**

No.	Structure	Formula	MW	Yield[a] (%)	Mp	NMR (400 MHz)	LC/MS (ES+)
13		$C_{17}H_{15}NO_4$	297	95	Oil	$CDCl_3$ δ 2.60 (dd,1H, $J = 2.4$,18.8Hz), 2.98 (br,1H), 3.05 (dd,1H, $J = 7.2$, 18.8 Hz),4.13 (s,3H), 5.30 (br,1H), 7.00 (d,1H,$J = 8.0$ Hz),7.07 (t,1H, $J = 7.2$ Hz), 7.26 (d,1H, $J = 7.2$ Hz), 7.48 (t,1H), 7.56 (t,1H, $J = 8.0$ Hz), 8.16 (d,1H, $J = 8.0$ Hz), 8.72 (d,1H, $J = 8.8$ Hz)	298 (M + 1) >98% pure
14		$C_{16}H_{11}Cl_2NO_3$	336	93	Oil	$CDCl_3$ δ 2.64 (dd, 1H, $J = 2.4$, 18.8 Hz), 3.13 (dd, 1H, $J = 6.8$, 18.8 Hz), 5.40 (m, 1H), 7.34 (dd, 1H, $J = 2.4$, 8.4 Hz), 7.40 (s, 1H), 7.48 (d, 1H, $J = 1.6$ Hz), 7.62 (d, 1H, $J = 7.6$ Hz), 7.70 (t, 1H, $J = 7.2$ Hz), 8.64 (d, 1H, $J = 8.8$ Hz)	337 (M + 1) >95% pure

15		$C_{14}H_{16}N_2O_4$	276	82	Oil	$CDCI_3$ δ 2.59 (br,1H), 2.66 (dd,1H, $J = 2.4$, 18.8 Hz), 3.09 (dd,1H, $J = 6.8$,18.8 Hz), 3.24 (t,2H, $J = 4.8$ Hz), 3.56 (t,2H, $J = 5.2$ Hz), 3.66 (t,2H, $J = 4.4$ Hz), 5.40 (br,1H), 7.21 (d,1H, $J = 8.0$ Hz), 7.58 (t,1H, $J = 7.6$ Hz), 8.30 (d,1H, $J = 8.4$ Hz)	277 (M + 1) 90% pure
16		$C_{15}H_{13}NO_4S$	303	89	Oil	$CDCl_3$ δ 2.71 (dd, 1H, J = 2.4, 18.8 Hz), 3.14 (dd, 1H, J = 6.8, 18.8 Hz), 5.40 (dd, 1H), 7.32 (d, 1H), 7.53 (m, 4H), 8.01 (d, 1H, J = 7.2 Hz), 8.60 (d, 1H, J = 8.4 Hz)	304 (M + 1) >95% pure

[a]Isolated yields.

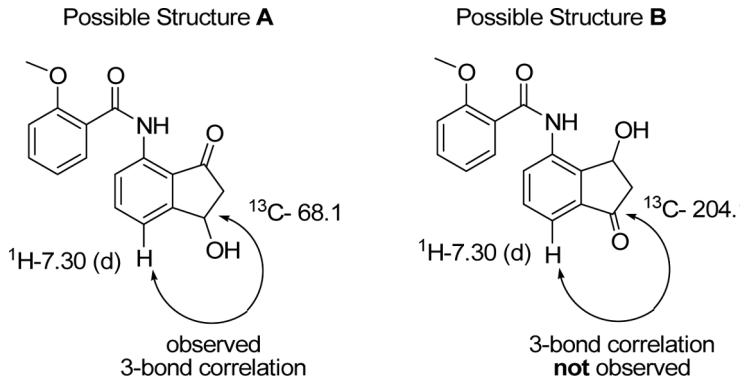


Figure 2. HMBC experiment results.

correlation (HMBC) spectral study. A correlation existed between the proton at 7.30 ppm and the carbon at 68.1 ppm, but no correlation was observed between any of the aromatic protons and the carbonyl carbon at 204.1 ppm. Only in structure **A** can both of these observations be accommodated. Thus, these experiments confirm that the structure of compound **13** is correct as depicted in Table 1 and, importantly, that the structure of compound **7** is also correct as shown in this report.

CONCLUSION

This report describes a concise and efficient synthesis of 7-amino-3-hydroxyindan-1-one (**7**), which will be useful as a three-dimensional, three-point scaffold for the preparation of biologically active compounds. In addition, the structure of scaffold **7** has been unambiguously determined using HMBC. A related scaffold, (chiral) 3-hydroxy-indan-1-one, is found in indatraline,[17] a nonselective monoamine reuptake inhibitor. An efficient enzymatic kinetic resolution process has been described for the preparation of both enantiomers[18] of this scaffold. This enzymatic transesterification procedure should also be applicable for the preparation of the enantiomers of **7**.

EXPERIMENTAL

All melting points were obtained in open capillary tubes and are uncorrected. The ^{1}H spectra were determined on a 400-MHz Inova Varian FT-NMR, with chemical shifts reported in parts per million (PPM) (δ) relative to tetramethylsilane (TMS) as internal standard. LC/MS were

measured on a Waters Micromass *Quattro* Ultima instrument, and both ultraviolet and ELSD detection modes were used.

Ethyl 4-Nitroindan-1,3-dione-2-carboxylic Acid (10)

To a solution of 3-nitrophthalic anhydride (5.79 g, 30.0 mmol) in methylene chloride (100 mL), ethyl acetoacetate (4.68 mL, 36.0 mmol) was added followed by acetic anhydride (5.65 mL, 60.0 mmol). To this reaction mixture triethylamine (12.5 mL, 90.0 mmol) was added dropwise over a 15-min period. The reaction mixture was stirred for 15 min and concentrated, and the residue was dissolved in water (250 mL) and cooled to 0 °C. Acidification by the dropwise addition of 2 N hydrochloric acid gave an orange precipitate, which was collected and air-dried to give 6.75 g (85%) of **10**, mp 152–154 °C. ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, 3H), 4.40 (m, 2H), 5.18 (br s, 1H), 7.60–7.98 (m, 3H). LC/MS 264.3 (ES+), 262.6 (ES−), purity 100% (UV and ELSD).

4-Nitroindan-1,3-dione (11)

To a solution of ester **10** (6.75 g, 25.7 mmol) in acetonitrile (300 mL) trifluoracetic anhydride (2.17 mL, 28.2 mmol) was added dropwise at rt. The reaction mixture was stirred for 45 min and concentrated. The residue was triturated with 1:1 chloroform:hexanes to produce a light brown solid, which was collected and air-dried to give 4.45 g (91%) of **11**, mp 130–132 °C (rep.[16] mp 133 °C). ^{1}H NMR ($CDCl_3$) δ: 3.38 (m, 2H), 7.98 (t, 1H), 8.10 (d, 1H), 8.22 (d, 1H). LC/MS 190.4 (ES−), purity 100% (UV and ELSD).

7-Amino-3-hydroxyindan-1-one (7)

To a solution of indanedione **11** in methanol (200 mL) under a nitrogen atmosphere, 10% Pd/C (100 mg) was added. The reaction flask was flushed with hydrogen, and a hydrogen balloon was added to the neck of the flask. Stirring was continued for 24 h. The catalyst was removed by filtration through Celite. The Celite pad was washed with methanol, and the filtrate was concentrated. Trituration of the residue with chloroform gave a light brown solid, which was collected and dried to give 1.24 g (76%) of **7**, mp 94–96 °C. ^{1}H NMR (acetone-d_6) δ: 2.40 (d, 1H), 2.88 (d, 1H), 4.58 (br s, 1H), 2.88 (d, 1H), 4.58 (br s, 1H), 5.22 (m, 1H), 6.24 (br s, 2H), 6.61 (d, 1H), 6.79 (d, 1H), 7.36 (t, 1H). LC/MS 154.3 (ES+), purity 100% (UV and ELSD).

General Method for the Preparation of Compounds 13–16

A solution of aminoindanone **7** (120 mg, 0.736 mmol) in 1,2-dichloroethane (20 mL) was equally distributed into four Teflon screw-capped vials (15 mL capacity). To each vial, corresponding acid chlorides of phenylsulfonyl chloride or 4-morpholinecarbonyl chloride (0.21 mmol each) were added, followed by diisopropylethylamine (DIEA) (75 μL, 0.037 mmol each). After capping, the solutions were shaken on a reaction block at room temperature overnight. The solutions were washed with sat. $NaHCO_3$ (2 mL), H_2O (2 mL), and dried (Na_2SO_4) and purified by column chromatography [90:10 dichloromethane (DCM):EtOAc or 50:50 hexane:EtOAc] to obtain the corresponding products (82–95%) as semisolids.

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