Synthesis of Aryl 2-(2-Imidazolyl)ethyl Ketones [1]

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The Claisen-Schmidt condensation of 1-(triphenylmethyl)-2-imidazolecarboxaldehyde with acetophenones yielded 1-aryl-3-[1-(triphenylmethyl)-2-imidazolyl]propen-1-ones **7**. Selective catalytic hydrogenation over platinum of **7** furnished 1-aryl-3-(2-imidazolyl)-1-propanones **8**. An alternate synthesis of **8** started with sodium borohydride reduction of **7** to give allylic alcohols, 1-aryl-3-[1-(triphenylmethyl)-2-imidazolyl]-2-propen-1-ols **10**, which were rearranged by hot aqueous sodium to **8**. Acid hydrolysis of **8** provided the title compounds and triphenylmethanol.

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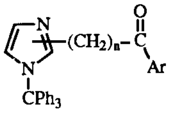
Syntheses of relatively few aryl ω-(*C*-imidazolyl)alkyl ketones **1** have been reported and we have set out to develop preparations of such compounds. Structurally, we required a number of aromatic ketones in which the keto group is separated by one to four methylene groups from one of the ring carbons of imidazole. The simplest members of this type are the well-known 2-phenacylimidazoles [2,3], in which the ketone is separated from imidazole (at *C*-2) by one methylene group. This paper specifically addresses the problem of synthesizing aromatic ketones which are linked to *C*-2 of imidazole by two methylene groups. A prototype of **1** was synthesized by King [4] who condensed 1-trityl-5-methyl4-imidazolecarboxaldehyde (trityl is triphenylmethyl, CPh_3) first with 3-acetyl-1-methylindazole to obtain an α,β-unsaturated ketone. Catalytic hydrogenation (2 days) of the alkene and the trityl group then furnished **2**.



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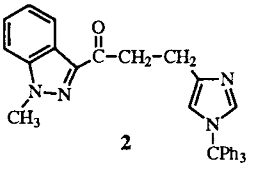

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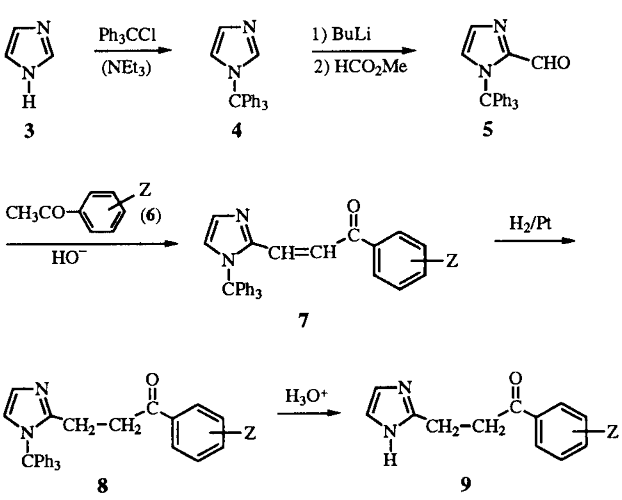
The methodology in King's patent provided the impetus to apply such a series of reactions to the synthesis of related aryl 2-(2-imidazolyl)ethyl ketones **9**. A cognate sequence would commence with a Claisen-Schmidt reaction of an appropriate 2-imidazolecarboxaldehyde and acetophenone to generate the corresponding α,β-unsaturated ketone. Unfortunately, the condensation of 2-imidazolecarboxaldehyde, *per se*, with acetophenone in the presence of a basic catalyst, in aqueous or non-aqueous media, produced intractable tars. In retrospect, this is perhaps not surprising since 2-imidazolecarboxaldehyde has been reported to be quite unstable in base [5]. Therefore, it is essential to mask the imidazole ring nitrogen by a suitable *N*-protective group before attempting Claisen-Schmidt condensations. Hence, we had to choose from a vast array of different protective groups of the imidazole ring nitrogen [6] in order to prepare a suitable 1-substituted-2-imidazolecarboxaldehydes. We gave some consideration to *N,N*-dimethylsulfamoyl as an *N*-protective group since this group can be removed by either mild acid or base [7]. However, since 1-(*N,N*-dimethylsulfamoyl)-imidazole is converted to the corresponding 2-carboxaldehyde in only about 20% yield [5], another *N*-protective group needed to be chosen.

We settled for the trityl group to help achieve our synthetic goal (Scheme 1). 1-Tritylimidazole (**4**) is well-known being readily prepared from imidazole (**3**). Furthermore, the trityl group is removed relatively easily by either acids or catalytic hydrogenation. Lithiation of **4** with *n*-butyllithium takes place readily at *C*-2 and subsequent formylation with methyl formate provided 1-trityl-2-imidazolecarboxaldehyde (**5**) in excellent yield [8-10]. Previously reported formylations of **4** utilized dimethylformamide (instead of methyl formate) to prepare **5** [11].

Scheme 1

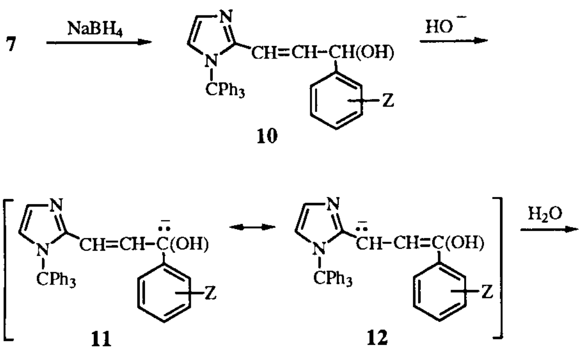


Where in **a**, Z = 4-Cl
b, Z = 2,4-Cl_2

The base-catalyzed Claisen-Schmidt condensation of **5** with aromatic methyl ketones **6** furnished α,β-unsaturated ketones (**7**). The aromatic ketones chosen were either 4-chloro- or 2,4-dichloroacetophenone and the condensation of **5**, using the method of Wattanasin and Murphy [12] gave rise to **7**, in excellent yields. No attempt was made to establish the ratio of *E* and *Z* isomers of **7**, nor were attempts made to separate the stereoisomers. The reduction of the conjugated double bond of **7** was accomplished in two different ways. Initially, catalytic reductions of **7** were somewhat temperamental and produced mixtures, but finally conditions were worked out whereby hydrogen and a platinum catalyst produced **8** in good yield. The trityl protective group remained intact but was removed independently from **8** by hot hydrochloric acid to furnish **9** (in good yield), along with (readily separated) triphenylmethanol.

An alternate route of **7** to **8** was explored, also (Scheme 2). Sodium borobydride reduction of **7** led to the allylic alcohols **10**. Based on reported rearrangements [13,14] of aromatic allylic alcohols of this type, **10** was converted to **8** in good yields. Essentially, this rearrangement hinges on the abstraction of a benzylic hydrogen of **10** to form **11**, whose resonance hybrid **12** is the enolate anion of **8**. Acidification of the reaction mixture yielded **8**.

Scheme 2



Where in **a**, Z = 4-Cl
b, Z = 2,4-Cl_2

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton and carbon-13 nuclear magnetic resonance (nmr) spectra (at 300 and 75.4 MHz, respectively) were recorded in deuteriochloroform on a Varian XL-300 spectrometer. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are designated as singlets (s), doublets (d), triplets (t), multiplets (m), if broad, by br. Aromatic carbon or proton signals associated with benzenoid systems are designated by Ar, and those with imidazoles, by Im.

Research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, and were used as supplied. Anhydrous reagents were purchased packaged under nitrogen gas in sure sealed bottles and were used directly. *n*-Butyllithium was used a 2.5 *M* solution in hexanes which was provided in sealed bottles (under nitrogen). Petroleum ether refers to that fraction boiling between 30-60°. Evaporation of solvents, *in vacuo*, implies their removal by means of a rotary flash evaporator using a water pump (20-30 torr) at about 40°. Thin layer chromatograms were run on precoated silica gel (supported on aluminum or polyester support, from Aldrich, 60 F_{254}) unless it is stated to be on alumina (E. Merck, neutral alumina 60 F_{254}). Elemental analyses were carried out by Midwest Microlab, Indianapolis, IN.

1-Tritylimidazole (4).

Of the many procedures available for the tritylation of imidazoles [*e.g.*, sodium hydride (or other bases) in *N,N*-dimethylformamide], we adopted from the one published by Bernabé and Burger [8], similar to one used recently by Pedersen and Berkowitz [15], which employed triethylamine in methylene chloride. To a cold (0 to -5°) stirred solution of imidazole (50.0 g, 0.73 mole) and triethylamine (104 ml, 0.75 mole) in methylene chloride (1 l) was added to a solution of trityl chloride (209 g, 0.75 mole) in methylene chloride (500 ml) over 30 minutes. After stirring at room temperature (3 hours), the mixture was filtered. The filtrate was washed with water (2 x 200 ml), dried (magnesium sulfate) and the solvent was evaporated, *in vacuo*. The colorless solid was recrystallized from ethanol to give **4** (196.5 g, 87%), mp 220-221°, lit mp 229-230° [16], 228° [17]; tlc: R_f = 0.15 (ethyl acetate-hexane, 1:1); ^{1}H nmr: δ for Im, 6.83 (H-5), 7.07 (H-4), 7.47 (H-2) as three t's (J = 1.2 Hz); for Ar, 7.12-7.20 (m, 6H), 7.29-7.38 (m, 9H); ^{13}C nmr: δ 75.0 (*C*Ar$_3$); for Im, 121.5 (C-5), 128.2 (C-4), 138.9 (C-2); for Ar, 127.9 [two carbons, rel intensity, of CH types (APT)], 129.6, 142.4.

1-(Triphenylmethyl)-2-imidazolecarboxaldehyde (5).

The reaction was carried out under dry nitrogen. To a cooled (-15 to -10°) stirred solution of 1-tritylimidazole (40.0 g, 0.129 mole) in anhydrous tetrahydrofuran (1300 ml) was added dropwise a cold 2.5 *M* solution of *n*-butyllithium in hexane (62.0 ml, 0.155 mole) over 9 minutes at -12°. The mixture was allowed to warm to room temperature and allowed to stand for 1 hour. The ^{1}H nmr spectral data indicated that litihiation at *C*-2 was complete (with the disappearance of the signal at δ 7.47). The reaction mixture was cooled again (-10°) and anhydrous methyl formate (24.0 ml, 0.38 mole) was added over 5 minutes. The mixture stood at room temperature for 4 hours. After quenching with aqueous sodium carbonate solution (60 ml), the *p*H was 7 and the solvent was evaporated, *in vacuo*. The residue was extracted with methylene chloride (2 x 600 ml), the extract dried (magnesium sulfate) and evaporated, *in vacuo*. The product was recrystallized from ethyl acetate (350 ml) to provide **5** as a pale yellow solid (46.5 g, quantitative), mp 185-187°, lit [11] mp 189-190°; tlc: R_f = 0.72 (ethyl acetate-hexane, 4:1), 0.95 (ethyl acetate-methanol, 24:1); ^{1}H nmr: (resembles the data reported at 60 MHz by Kirk [11]), δ for Im 7.04 (d, H-5, J = 1.1 Hz), 7.29 (d, H-4, J = 1.1 Hz); for Ar, 7.07-7.19 (m, 6H), 7.25-7.30 (m, 9H), 9.23 (s, CHO); ^{13}C nmr: δ, 76.88 (*C*Ph$_3$), for Im, 126.9 (C-5), 128.6 (C-4), 142.0 (C-2); for Ar, 128.0, 128.2, 129.5, 142.0; 178.6 (C=O).

1-(4-Chlorophenyl)-3-(1-trityl-2-imidazolyl)-2-propen-1-one (7a).

The method for the Claisen-Schmidt reaction in this system is an adaptation of the one published by Wattanasin and Murphy

[12]. A solution of 4-chloroacetophenone [10.5 g (8.82 ml), 0.0672 mole] in anhydrous ethanol (150 ml) was stirred at room temperature with sodium hydroxide pellets (20 g) for 10 to 15 minutes, after which 1-trityl-2-imidazolecarboxaldehyde (25.0 g, 0.0739 mole) was added, in several portions (2-5 minutes). After stirring at room temperature (2 hours), the thick yellow suspension was filtered, the product washed with ethanol, then water, dried to provide pure **7a** (20.6 g, 59%), mp 172-173°; tlc: $R_f = 0.95$ (ethyl acetate-methanol, 24:1); ^{1}H nmr: δ 6.81, 7.59 (d's, *trans* CH=CH, J = 15.1 Hz), 6.93 (d, Im H-5, J = 1.2 Hz, only discernible Im signal), other Ar*H*, 7.09-7.18 (m, 7H), 7.28-7.34 (m, 11H), 7.71 (m, 1H); ^{13}C nmr: δ 75.9 (*C*Ph$_3$), 122.3, 124.9, 128.2, 128.4, 128.6, 129.7, 129.8, 132.9, 136.0, 138.8, 142.4, 145.2, 149.8 (C=C, Ar and Im C's), 188.5 (C=O).

Anal. Calcd. for $C_{31}H_{23}ClN_2O$: C, 78.38; H, 4.88; N, 5.89. Found: C, 78.75; H, 4.88; N, 5.94.

1-(2,4-Dichlorophenyl)-3-(1-trityl-2-imidazolyl)-2-propen-1-one (**7b**).

A suspension of **5** (5.0 g, 0.015 mole) and **6b** (2.85 g, 0.015 mole) in absolute ethanol (25 ml) containing 4-6 sodium hydroxide pellets (1.0-1.2 g) was stirred at 25° (2 hours). The reactants dissolved and were replaced by a thick suspension. The fine yellow solid was filtered, washed with 50% aqueous ethanol, then cold water, and was dried. The product weighed 6.0 g (80%), mp 138-140°, unchanged upon crystallization from ether; tlc: $R_f = 0.95$ (ethyl acetate-methanol, 24:1); ^{1}H nmr: δ 6.28 (d, *trans* CH=CH, J = 15.6 Hz), 6.76 (d, *cis* CH=CH, J = 8.4 Hz), 6.90-7.35 (alkenyl and aromatic H's).

Anal. Calcd. for $C_{31}H_{22}Cl_2N_2O$: C, 73.09; H, 4.35; N, 5.49. Found: C, 72.72; H, 4.31; N, 5.51.

1-(4-Chlorophenyl)-3-(1-trityl-2-imidazolyl)-2-propen-1-ol (**10a**).

The yield of this reaction was improved remarkably when sodium hydroxide was added to the reaction mixture. To a solution of sodium borohydride (0.08 g, 0.0022 mole) in methanol (70 ml), containing 12 *N* sodium hydroxide (5 ml), was added **7a** (2.0 g, 0.0042 mole). The stirred mixture was refluxed (4 hours) and solvents were evaporated almost to dryness, *in vaccuo*. The residue was triturated with cold water to furnish a gum, product, which was separated and washed with water. Upon drying, the product (1.9 g, 95%) solidified, mp 78-80°; tlc: $R_f = 0.55$ (ethyl acetate-methanol, 24:1); ^{1}H nmr: δ, 4.70 (m, C*H*OH), 5.55 (d, one of the *trans* CH=CH, J = 15.6 Hz), 6.50-6.59 (m, *cis* CH=CH); for Im, 6.70 (d, H-5, J = 1.2 Hz), 6.91 (d, H-4, J = 1.2 Hz); for Ar and alkene H's, 7.00-7.36 (m).

Anal. Calcd. for $C_{31}H_{25}ClN_2O \bullet H_2O$: C, 75.21; H, 5.49; N, 5.66. Found: C, 75.40; H, 5.29; N, 5.64.

1-(2,4-Dichlorophenyl)-3-(1-trityl-2-imidazolyl)-2-propen-1-ol (**10b**).

A stirred solution of **7b** (5.0 g, 0.01 mole), sodium borohydride (0.2 g, 0.005 mole) in methanol (300 ml) was added 12 *N* sodium hydroxide (20 ml) and the mixture was refluxed for 4 hours. The solution was concentrated, *in vacuo*, to about one tenth of its original volume and the residue was triturated with cold water (50 ml). The product (5.0 g, 99%) was filtered, washed with water and dried, mp 82-85°. The alcohol tended to retain water and had to be dried thoroughly at 80°, *in vacuo*, for microanalysis; tlc: $R_f = 0.45$ (ethyl acetate-methanol 24:1); ^{1}H nmr: δ 5.28 (d, C*H*OH, J = 5.4 Hz), 5.52 (d, one half of *trans* CH=CH, J = 15.6 Hz), 6.58-6.65 (m, *cis*-CH=CH), 6.69 (d, Im H-5, J = 1.3 Hz), 6.89 (d, Im H-4, J = 1.3 Hz), 7.00-7.30 (m, alkenyl and aromatic H's).

Anal. Calcd. for $C_{31}H_{24}Cl_2N_2O$: C, 72.80; H, 4.73; N, 5.48. Found: C, 72.49; H, 4.93; N, 5.36.

1-(4-Chlorophenyl)-3-(1-trityl-2-imidazolyl)-1-propanone (**8a**).

Method A: Catalytic Hydrogenation of **7a**.

Hydrogenation of **7a** (3.0 g, 6.32 mmoles) was conducted in ethanol (250 ml), using 5% platinum on charcoal (2.5 g) and at 35 psi (2.5 hours). The catalyst was filtered off and the solvent removed, *in vacuo*. The residue was triturated with acetonitrile (50 ml) to provide colorless **8a** (2.4 g, 80%), mp 161°; tlc: $R_f =$ 0.80 (ethyl acetate-methanol, 24:1); ^{1}H nmr: δ 2.36, 2.78 (t's, CH$_2$'s, J = 7.5 Hz), 6.77 (d, Im H-5, J = 1.4 Hz), 6.95 (d, Im H-4, J = 1.4 Hz), a series of multiplets for aromatic H's, 7.12-7.23 (6H), 7.25-7.43 (11H), 7.73 (2H); ^{13}C nmr: δ 22.5 (*C*H$_2$C=O), 37.2 (*C*H$_2$Im), 198.7 (C=O).

Anal. Calcd. for $C_{31}H_{25}Cl_2N_2O$: C, 78.05; H, 5.28; N, 5.87. Found: C, 77.68; H, 5.43; N, 6.12.

Method B: By Rearrangement of **10a**.

To a stirred solution of **10a** (1.0 g, 0.0021 mole) in methanol (40 ml) containing potassium hydroxide (6.0 g) was added water (10 ml) at the reflux. After 24 hours, **8a** separated and was filtered from the warm mixture, washed with 80% aqueous methanol and dried (0.60 g, 60%), mp 161°, identical to the sample made by Method A (nmr).

1-(2,4-Dichlorophenyl)-3-(1-trityl-2-imidazolyl)-1-propanone (**8b**).

Method A. Catalytic Hydrogenation of **7b**.

A solution of **7b** (5.0 g, 0.001 mole) in ethanol (300 ml), containing 10% platinum on charcoal catalyst (0.8 g), was hydrogenated for 4 hours at room temperature (35 psi). The mixture was filtered and the solvent was evaporated, *in vacuo*. The residue was triturated with methanol (15 ml) and the colorless solid filtered, washed with methanol and dried to give **8b** (4.0 g, 80% yield), mp 152°; tlc: $R_f = 0.70$ (ethyl acetate); ^{1}H nmr: δ 2.31, 2.77 (two t's, CH$_2$'s, J = 7.4 Hz), 6.75 (d, Im H-5, J = 1.4 Hz), 6.92 (d, Im H-4, J = 1.4 Hz), 7.13-7.40 (m, ArH).

Anal. Calcd. for $C_{31}H_{24}Cl_2N_2O \bullet H_2O$: C, 70.30; H, 4.95; N, 5.29. Found: C, 70.59; H, 4.81; N, 5.19.

Method B. By Rearrangement of **10b**.

The allylic alcohol **10b** (2.0 g, 0.004 mole) and potassium hydroxide pellets (85%, 12.0 g) were dissolved in hot methanol (40 ml). At the reflux, boiling water (10 ml) was added slowly (so that no precipitate was present) and the mixture was refluxed for 24 hours. The colorless solid was filtered from the hot mixture, washed with a cold mixture of methanol and water (4:1) and was dried. The ketone weighed 1.3 g (60%), mp 150-153° and was identical to that obtained from Method A.

1-(4-Chlorophenyl)-3-(2-imidazolyl)-1-propanone (**9a**).

The protective trityl group was removed by modification of the method published by Kirk [11]. A solution of **8a** (7.7 g, 0.0161 mole) in methanol (150 ml), containing concentrated hydrochloric acid (6 ml), was refluxed (2 hours), then evaporated to dryness, *in vacuo*. Addition of concentrated hydrochloric acid (5 ml) and water (50 ml) caused a colorless solid to precipitate

(4.20 g, 100%) which was identified as triphenylmethanol (^{1}H nmr, δ 7.35-7.38 (m, Ar*H*), 3.00 (broad s, OH), mp 162-164°, identical to an authentic sample from Aldrich Chemical Company). The acidic filtrate was extracted with methylene chloride (2 x 200 ml) and then make alkaline (*p*H 8) with a saturated solution of sodium bicarbonate. The product **9a**, (3.38 g, 82%) was filtered, washed with water and dried, mp 115-117°; tlc: $R_f = 0.40$ (ethyl acetate-methanol, 4:1), 0.73 (alumina, ethyl acetate-methanol, 24:1); ^{1}H nmr: δ 3.17, 3.44 (2 t, CH_2's, J = 6.6 Hz), 6.94 [s, Im H-4(5)], 7.43, 7.89 (m, AA'BB', Ar*H*).

Anal. Calcd. for $C_{12}H_{11}ClN_2O \cdot 0.25H_2O$: C, 60.25; H, 4.85; N, 11.71. Found: C, 60.73; H, 4.71; N, 11.54.

1-(2,4-Dichlorophenyl)-3-(2-imidazolyl)-1-propanone (9b).

A solution of ketone **8b** (1.0 g, 0.002 mole) in 5% acetic acid in methanol (30 ml), containing concentrated hydrochloric acid (1 ml), was refluxed for 90 minutes, evaporated, *in vacuo,* and the residue was diluted with water (1 ml) and concentrated hydrochloric acid (1 ml). Extraction with methylene chloride (2 x 50 ml) furnished triphenylmethanol (0.4 g, 77%). After adjusting the *p*H to 8, and extracting with methylene chloride (3 x 70 ml), there was isolated a yellow oil. Addition of the minimum amount of ether, followed by hexane afforded a colorless solid (0.4 g, 79%), mp 90-93°; tlc: $R_f = 0.59$ (ethyl acetate-methanol, 7:3), 0.83 (alumina, ethyl acetate-methanol, 24:1); ^{1}H nmr: δ 3.13, 3.38 (t, CH_2's, J = 6.6 Hz), 6.92 [s, Im H-4(5)], 7.20-7.42 (m, Ar*H*), 10.52 (br s, NH).

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O$: C, 53.55; H, 3.75; N, 10.41. Found: C, 53.30; H, 3.90; N, 10.60.

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