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The Synthesis of Substituted 2-Aminophenyl Heterocyclic Ketones

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THE SYNTHESIS OF SUBSTITUTED 2-AMINOPHENYL HETEROCYCLIC KETONES

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Abstract: The synthesis of substituted 2-aminophenyl heterocyclic ketones, key intermediates to the preparation of 1,4-benzodiazepines has been achieved in one step and in good, yield from the corresponding anthranilic acid, by treatment with heterocyclic lithium reagents and chlorotrimethylsilane.

In relation to other work, 5-(2-heteroaryl)-1,4-benzodiazepines[1,2] were employed as bidentate ligands to form the platinum complexes. The key intermediates leading to the synthesis of these ligands were the previously described[1-3] substituted 2-aminophenyl heterocyclic ketones. Literature procedures required tedious multi-step synthesis, and some procedures were limited by their lack of the general utility. We have now applied a recently developed ketone synthesis from carboxylic acid that uses the lithium reagents and chlorotrimethylsilane[4] and synthesized the substituted 2-aminophenyl heterocyclic ketones listed in Scheme III in one step.

The representative literature methods previously used for the synthesis of 2-aminophenyl heterocyclic ketones are outlined in the Schemes I and II. By the addition of a heterocyclic lithium salt to 2-nitrobenaldehyde with subsequent

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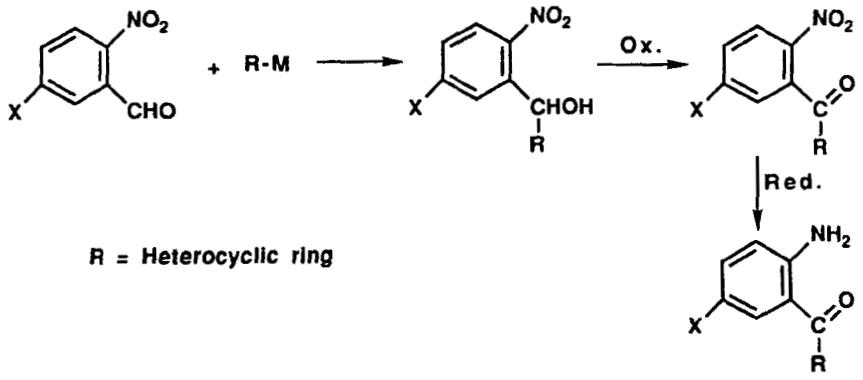
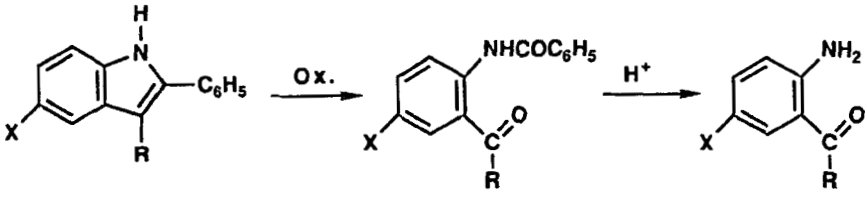
Scheme I



R = Heterocyclic ring

Scheme II



R = Heterocyclic ring

oxidation of the alcohol and reduction of the nitro group, Kalish and co-workers[2] employed the three-step reaction shown in scheme I to furnish the appropriate 2-aminophenyl heterocyclic ketones. Alternatively, 2-aminophenyl heterocyclic ketones were obtained by oxidative fission of the 2,3-double bond of 3-heterocyclic substituted indoles, followed by hydrolysis of the oxidation product, as shown in Scheme II. However, the indole intermediate used, required a multi-step synthesis from the corresponding phenacyl heterocyclic compounds, by means of a Fisher *indole synthesis*[5].

A literature reported[4] that the high yield preparation of aliphatic ketones without the formation of corresponding carbinols could be accomplished by the

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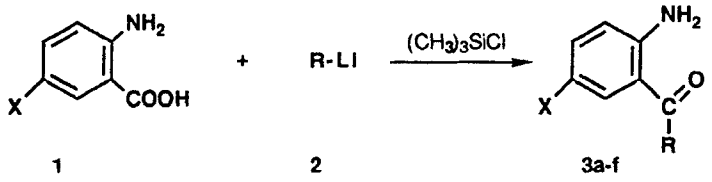
Scheme III



1 2 3a-f

		% yield
3a	R = 2-Pyridyl, X = Cl	58
b	R = 1-Methyl-2-imidazolyl, X = Cl	60
c	R = 2-Fural, X = Cl	49
d	R = 2-Thiophenyl, X = Cl	54
e	R = 2-Pyridyl, X = I	31
f	R = 2-Pyridyl, X = H	63

sequential treatment of a carboxylic acid with an alkyl lithium reagent and chlorotrimethylsilane. This appeared to offer a promising alternative, one step synthetic approach to aminophenyl-heterocyclic ketones. We have applied this methodology to a number of different heterocyclic lithium reagents, modifying the original procedure to accommodate the different substrates. It was found that the various ketones could be obtained by this one step synthesis, in moderate to good yield, as shown in Scheme III. The optimization of reaction stoichiometry was carried out for compound 3a. The best yields were obtained using a minimum of four equivalents of lithium base. The use of more than four equivalents did not show any improvement in the yield, but the use of less than four equivalents of the base gave poor yields of product (e.g., only 11% yield of 3a was obtained by using 3 equivalents lithium base).

Experimental:

Melting points were determined with the Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were taken either on a Bruker WP-200SY, or on a

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Varian 400 Fourier transform spectrometer. Flash chromatography was performed using Kieselgel 60 (230-400 mesh). Diethyl ether and THF were distilled from sodium benzophenone ketyl and chlorotrimethylsilane was freshly distilled before use. All glassware was stored at 150 °C overnight and assembled while hot under a nitrogen atmosphere. All other chemicals were used as received.

2-(2-Amino-5-chlorobenzoyl)pyridine(3a).

A stirred solution of 1.25 M (titrated according to the literature procedure[6]) n-butyllithium in hexane (12.1 mL, 19.4 mmol) was treated dropwise at -40 °C with 2-bromopyridine (1.68 mL, 17.6 mmol) in dry diethyl ether (21 mL) over 0.5 hr. under a nitrogen atmosphere. The temperature was maintained at -40 °C during the addition. The resultant dark orange solution was stirred for a further 0.5 hr. at -40 °C.

In a separate flask, a solution of 2-amino-5-chlorobenzoic acid (0.68 g, 4.0 mmol) in dry THF (30 mL) also under a nitrogen atmosphere and at 0 °C (ice bath) was added in one portion to the solution prepared as described above, the mixture was stirred for 2 hr. at 0 °C and then treated with freshly distilled Me_3SiCl (10 mL, 80 mmol) while the stirring continued. The reaction mixture was allowed to warm to room temperature (ca. 10 min.) and hydrolyzed with 1N HCl (30 mL). The resulting two-phase system was separated. The aqueous phase was neutralized with 3N NaOH solution and extracted with diethyl ether (3 x 50 mL). The combined organic extractions were dried over Na_2SO_4 and the solvent was evaporated. The resulting yellow oil was purified by the flash chromatography (5cm x 15cm) using ethyl acetate:hexane (3:7; v/v) as eluent. Crystallization of the product from a methylene chloride/hexane mixture gave 0.51g (58%) of 2-(2-amino-5-chlorobenzoyl)pyridine as yellow needle-like crystals (mp 144-145 °C; lit.[1] 145-146 °C). ^{1}H NMR δ6.85(d, J = 9 Hz, 1H); 7.33(dd, J = 9, 2.6 Hz, 1H);

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7.45(br, 2H); 7.55(d, J = 2.5 Hz,1H); 7.65(td, J = 4.8, 1.1 Hz,1H); 7.8(d, J = 7.8 Hz, 1H); 8.50(td,J = 7.7, 1.7 Hz, 1H); 8.70(dd, J = 4.1, 1.0 Hz, 1H).

2-Amino-5-chlorophenyl 1-methyl-2-imidazolyl ketone(3b).

Following the above procedure, a lithium solution prepared from 1-methylimidazole (1.28 mL, 16 mmol) and 1.25 M n-butyllithium (14 mL,17.6 mmol) in 30 ml of dry THF was added to a solution of 2-amino-5-chlorobenzoic acid (0.34 g, 2 mmol) in dry THF (15 mL). The mixture was stirred for 2 hr. at 0 °C and quenched with 10 mL of chlorotrimethylsilane. After the work-up, the dark red oil was purified by flash chromatography using ethyl acetate:hexane (1:5, v/v) as eluent. Crystallization from methylene chloride/hexane mixture gave 2-amino-5-chlorophenyl 1-methyl-2-imidazolyl ketone as yellow needle-like crystals (0.27 g, 60%; mp 91-92 °C, lit.[2] mp 89-91 °C). ^{1}H NMR δ3.9(s, 3H); 6.85(d, J = 9.0 Hz, 1H); 7.2(d, J = 0.9 Hz, 1H); 7.3(m, 3H); 7.5(s, 1H); 8.6(d, J = 2.6 Hz, 1H).

2-Amino-5-chlorophenyl 2-furyl ketone(3c).

Furan (3.5 mL, 48 mmol) in 20 mL of dry diethyl ether was added dropwise to 1.25 M n-butyllithium in hexane (23 mL, 28 mmol) at about -20 °C and over 15 min.. After the addition the mixture was allowed to warm to room temperature, then refluxed for 8 hr.

A solution of 2-amino-5-chlorobenzoic acid (3.6 mmol, 0.61 g) in dry THF (15 mL) at 0 °C was treated with the lithium solution prepared above. The mixture was allowed to warm to room temperature and then refluxed for 8 hr. and then quenched with 10 mL of chlorotrimethylsilane. After work up, using the procedure described above, the yellow oil was purified by the flash chromatography using ethyl acetate:hexane (1:5, v/v) as eluent. Crystallization from methanol gave 2-amino-5-chlorophenyl 2-furyl ketone (0.3 g, 49%) as yellow needle-like crystals (

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mp 113-115 °C, lit.[3] 113-114 °C). ^{1}H NMR δ6.8(d, J = 1.5 Hz, 1H); 6.9(dd, J = 8.9, 1.8 Hz, 1H); 7.0(br, 2H); 7.3(dd, J = 9.2, 2.7 Hz, 2 H); 7.75(d, J = 2.0 Hz, 1H); 8.05(d, J = 1.3 Hz, 1H).

2-Amino-5-chlorophenyl 2-thienyl ketone(3d).

A solution of 2-bromothiophene (2.6 mL, 32.0 mmol) in dry THF (20 mL) was added dropwise to a solution of 1.25 M n-butyllithium in hexane (15 mL, 18.7 mmol) at -78 °C. The solution was warmed to 0 °C and stirred for half an hour.

In a separate flask, 2-amino-5-chlorobenzoic acid (0.34 g, 2.0 mmol) in dry THF (30 mL) was added the above lithium solution at -78 °C in one portion and stirred for 20 min. The solution was then warmed to room temperature, stirred for a further 48 hr. and quenched with Me_3SiCl (10 mL). Work-up of the reaction was the same as in the previous example. The yellow oil afforded was purified by the flash chromatography using a mixture of petroleum ether:ethyl acetate (8:1, v/v) as the eluent. Removal of solvent gave 2-amino-5-chlorophenyl 2-thienyl ketone (0.24 g, 54%) as yellow crystals (mp 95-97 °C, lit.[3] 94.5-96 °C). ^{1}H NMR δ 7.2(br, 2H); 7.35(d, J = 8.9 Hz, 1H); 7.75-7.85(m, 2H); 8.21(dd, J = 9.7, 2.4 Hz, 2H); 8.5(d, J = 5.0 Hz, 1H).

2-(2-Amino-5-iodobenzoyl)pyridine(3e).

A solution of 2-amino-5-iodobenzoic acid (1.1 g, 4.0 mmol) in dry THF (30 mL) at -40 °C was treated with a 2-pyridyllithium solution (17.6 mmol) prepared as described for **3a** above and quenched with Me_3SiCl (10 mL) after 2 hr. stirring at 0 °C. Following the same work-up and purification procedure described for **3a**, 2-(2-amino-5-iodobenzoyl)pyridine crystallized from a mixture of methylene chloride/hexane (0.40 g, 31%, mp 101-102°C) was obtained. ^{1}H NMR δ6.7(d, J = 8.8 Hz, 1H); 7.45(br, 2H); 7.5(dd, J = 8.9, 2.2 Hz, 1H); 7.6(td, J =

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4.7, 1.1 Hz, 1H); 7.8(m, 2H); 8.0(td, J = 6.7, 1.7 Hz, 1H); 8.65(dd, J = 4.8, 1.6 Hz, 1H); MS *m/z*(intensity) 324(47%), 296(87%), 295(100%), 246(18%), 197(12%). 2-(2-Aminobenzoyl)pyridine(**3f**) (0.1 g, 8%, mp 144-145 °C, lit.[7] 145-146 °C) was obtained as by-product (halo-metal exchange).

2-(2-Aminobenzoyl)pyridine(3f).

A solution of 2-aminobenzoic acid (0.55 g, 4.0 mmol) in dry THF (30 mL) at -40 °C was treated with 17.6 mmol of 2-lithiopyridine prepared as described above for **3a** and quenched with Me_3SiCl (10 mL) after 2 hr. stirring at 0 °C. Following the same work-up and purification procedure used in the previous example and crystallization of the product from methylene chloride/hexane afforded 2-(2-aminobenzoyl)pyridine (0.50 g, 63%; mp 144-145 °C, lit.[7] mp 145-146 °C). ^1H NMR δ6.45(td, J = 7.0, 1.2 Hz, 1H); 6.85(td J = 8.4, 0.8 Hz, 1H); 7.3-7.4(m, 4H); 7.6(m, 1H); 7.7(d, J = 7.8 Hz, 1H); 8.0(td, J = 7.7, 1.7 Hz, 1H); 8.65(dd, J = 4.1, 1.1 Hz, 1H).

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