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Approaches toward the preparative-scale synthesis of target 3,4-dihydro-1(2*H*)-isoquinolinones **1-3** are presented. Compounds **1** and **2** were prepared *via* a Schmidt rearrangement on easily obtained indanone precursors, but in low overall yield. A better method to make this class of compounds is exemplified by the large-scale synthesis of **2** *via* a Curtius rearrangement sequence. Thus, high-temperature thermal cyclization of an *in situ* formed styryl isocyanate from precursor **8** in the presence of tributylamine gave the corresponding 1(2*H*)-isoquinolinone (**9**). Catalytic hydrogenation of **9** provided the desired 3,4-dihydro-5-methyl-1(2*H*)-isoquinolinone (**2**) in 65 % overall yield. Similar reduction of a commercially available 5-hydroxy-1(2*H*)-isoquinolinone precursor **10** followed by an *O*-alkylation/amination sequence gave target **3** in good overall yield. The route proceeding *via* the Curtius rearrangement is recommended for large scale synthesis of other 3,4-dihydro-1(2*H*)-isoquinolinones. Only when deactivating substituents or sensitive functionality within the benzenoid ring render the high temperature ring closure of the intermediate isocyanate inefficient might a Schmidt rearrangement protocol be the method of choice.

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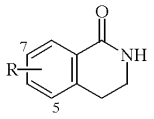
Introduction.

Previous reports [1-4] from our laboratories have described the synthesis and biological activity of a series of 3,4-dihydro-1(2*H*)-isoquinolinones as potent inhibitors of poly(ADP-ribose) polymerase (PARP), a chromatin-bound enzyme involved in the regulation of DNA repair. As part of these studies, we required operationally simple, and potentially high-yielding syntheses that would provide multigram quantities of three lead compounds **1-3** for expanded *in vivo* evaluation. To synthesize each of these previously unknown target molecules, we evaluated various methods reported in the literature to make closely related compounds. We describe herein the application of these methods toward the synthesis of our target compounds, and in some cases outline significant improvements over previous methodologies.

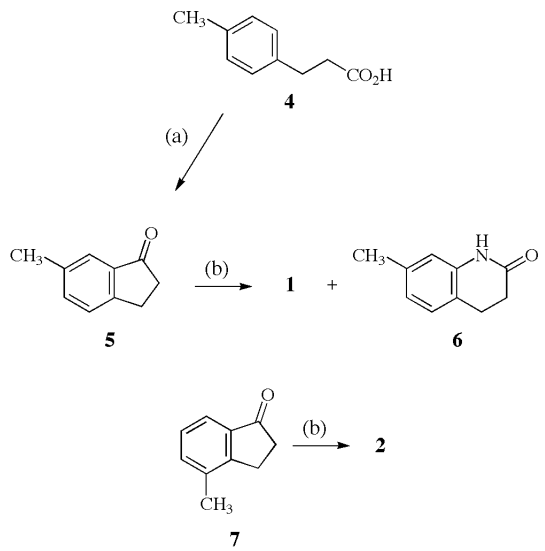


1: R = 7-CH_3
2: R = 5-CH_3
3: R = 5-$O(CH_2)_3NHCH_3$

Results and Discussion.

One general route to 3,4-dihydro-1(2*H*)-isoquinolinones proceeds *via* Schmidt rearrangement from appropriately substituted indanones, and is useful for the synthesis of compounds with a fairly broad range of benzenoid substituents. Depending on the substitution pattern, variable amounts of the isomeric 2(1*H*)-quinolinone and tetrazole side products are obtained as minor components of the reaction. This methodology was applied to our first target compound, 3,4-dihydro-7-methyl-1(2*H*)-isoquinolinone (**1**), which was synthesized as shown in Scheme 1.

Scheme 1



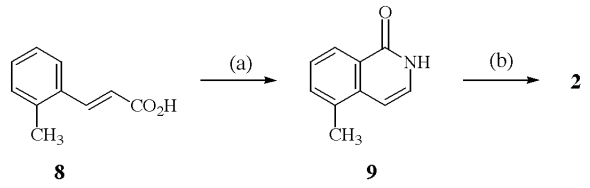
Reagents and conditions: (a) PPA; (b) NaN_3, CCl_3CO_2H.

Polyphosphoric acid ring closure of 3-(4-methylphenyl)-propanoic acid (**4**)[5] was performed by the method of Simchen and Krämer [6], but on a much larger scale to provide indanone **5** in 74% yield [7]. Indanone **5** was then subjected to the Schmidt rearrangement with sodium azide in trichloroacetic acid utilizing the procedure of Tomita and Minami [8] to provide the initial target **1** in 29% yield along with the known isomeric 3,4-dihydro-2(1*H*)-quinolinone

(**6**) [9,10] in 8% yield following flash silica gel chromatography. The application of the same Schmidt conditions to the isomeric 2,3-dihydro-4-methyl-1*H*-inden-1-one (**7**) [11] provided target compound **2** in 47% yield on a small scale. Recently there was a report [12] wherein the oxime tosylate of **7** was subjected to a variety of Beckmann rearrangement conditions under aluminum chloride catalysis. However, **2** was obtained in only 13% yield, with the balance of the product being the isomeric 2(1*H*)-quinolinone.

Because the above routes were poor yielding and generated a mixture of isomers, we decided to look for another approach to synthesize target compound **2**, which we required in much larger quantities. A review of the literature revealed that such a route was available *via* thermal cyclization of an appropriately substituted styryl isocyanate precursor as described by Eloy and Deryckere [13]. Indeed they described application of this reaction toward the synthesis of isoquinolinone **9** in 62% yield from acid **8** on a 0.4 mole scale as shown in Scheme 2.

Scheme 2

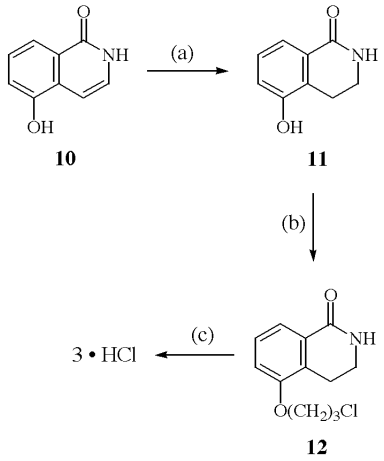


Reagents and conditions: (a) (i) $SOCl_2$, CH_2Cl_2(ii) NaN_3, aq. *p*-dioxane, 0° (iii) Ph_2O, Bu_3N, 230°; (b) H_2, 5% Pd/C, CH_3OH.

However, when we attempted to repeat this procedure on a 0.2 mole scale, we did not obtain any **9**, but instead an unidentified side product, mp 180-182° (acetone), that appeared to be a dimer by ^1H and ^{13}C NMR spectroscopy. The compound also displayed a strong carbonyl stretch at 1725 cm^{-1} in the infrared spectrum. Intrigued by a later report by these same investigators in which thermal cyclization of related isocyanates was performed as above but in the presence of tributylamine [14], we applied their general conditions on a 0.1 mole scale. Thus, reaction of the acid chloride of **8** with sodium azide gave the acyl azide, which was not isolated, but subjected to Curtius rearrangement to the corresponding isocyanate followed by ring closure in refluxing diphenyl ether/tributylamine. This gave the known 5-methyl isoquinolinone **9** [13,15] in 68% yield. The reaction was scaled up to 0.5 mole without any loss of yield. Following completion of our work, we became aware that the Curtius rearrangement/cyclization has been shown to proceed better for some 5-substituents using tetraglyme as a reaction solvent [16]. Standard catalytic hydrogenation of **9**, as described earlier [17], then provided the target 3,4-dihydro compound **2** in 95% yield. We briefly looked at other conditions that might selectively reduce the 3,4-double bond (hydrogenation over Raney nickel or 10% palladium on barium sulfate, sodium cyanoborohydride in acetic acid or trifluoroacetic acid, borane-pyridine/88% formic acid, and stannous chloride/concentrated HCl), but no reaction occurred under any of these conditions.

Since the C-5 position was determined to be optimal for inhibition of PARP [1], and target compounds **1** and **2** suffered from poor aqueous solubility, we synthesized a number of compounds with basic functionality appended to this position. Compound **3** was one analog with an outstanding *in vitro* profile, and thus multigram quantities of material were required for *in vivo* follow-up studies. Its scale-up synthesis was carried out as shown in Scheme 3.

Scheme 3



Reagents and conditions: (a) H_2, 20% Pd/C; (b) $Br(CH_2)_3Cl$, K_2CO_3; (c) (i) aq NH_2CH_3 (ii) HCl.

Catalytic hydrogenation of commercially available 1,5-dihydroxy-1(2*H*)-isoquinoline (**10**) on a 0.31 mole scale provided the 3,4-dihydro intermediate **11**[18] in 85% yield. Alkylation of **11** proceeded selectively onto the C-5 phenolic function by reaction of its potassium salt with 1-bromo-3-chloropropane in refluxing ethanol to give product **12** in 86% yield. Subsequent displacement of the side chain chloro function was then performed with 40% aqueous methylamine in methanol at 80° to give the target analog **3** in 64 % yield as the hydrochloride salt.

Conclusions.

We describe different methods for the preparative-scale synthesis of three target 3,4-dihydro-1(2*H*)-isoquinolinone PARP inhibitors. The best method in terms of simplicity and overall yields utilizes the catalytic hydrogenation of a suitable 1(2*H*)-isoquinolinone precursor. For cases in which such precursors are not commercially available for direct catalytic hydrogenation as shown in Scheme 3, the

most efficient and potentially most general route to their formation is *via* the Curtius rearrangement of an *in situ* formed acyl azide as exemplified in Scheme 2. Only when deactivating substituents or sensitive functionality within the benzenoid ring render the high temperature ring closure of the intermediate isocyanate inefficient might the Schmidt rearrangement protocol outlined in Scheme 1 be the method of choice.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Digilab FTS-14 or Nicolet MX-1 FTIR spectrometer. ^{1}H Nuclear magnetic resonance (^{1}H NMR) spectra were determined at 250 MHz on a Bruker AM250 instrument. Chemical shifts are reported as δ units downfield from internal tetramethylsilane on samples of ~1% w/v. Electron-impact mass spectra (EIMS) were obtained on a Finnigan TSQ70 mass spectrometer at 70 eV. Combustion analyses were determined on a CEC 440 Elemental Analyzer. Column chromatography was carried out in the flash mode utilizing E. Merck 230-400 mesh silica gel. Analytical tlc was carried out on E. Merck silica gel 60 F_{254} plates with detection by UV light. All reaction solvents were reagent grade or distilled-in-glass, and were stored over activated 3A (for lower alcohols) or 4A molecular sieves. Following normal workup procedures, organic extracts were dried over anhydrous sodium sulfate or magnesium sulfate prior to concentration.

2,3-Dihydro-6-methyl-1*H*-inden-1-one (**5**).

A solution of 94 g (0.57 mol) of 3-(4-methylphenyl)propanoic acid (**4**) [5] in 200 mL of dichloromethane was added portionwise during 2 hours to 2 kg of stirring polyphosphoric acid maintained at 80-90°. After the addition was complete, the mixture was heated for 3 hours. The orange solution was diluted with 3.5 L of ice-water and the precipitated solid was collected by suction filtration then washed with water. The crude product was dissolved in dichloromethane and the solution was washed with saturated aqueous sodium carbonate, decolorized with charcoal, and concentrated to give a white solid. Crystallization from hexanes afforded 62 g (74%) of **5**, mp 62.5-65° (lit [6] mp 58-60°).

3,4-Dihydro-7-methyl-1(2*H*)-isoquinolinone (**1**) and 3,4-Dihydro-7-methyl-2(1*H*)-quinolinone (**6**).

A mixture of 30 g (0.21 mol) of indanone **5** and 300 g of trichloroacetic acid was stirred at 65-70° until the mixture became homogeneous. Then 28 g (0.43 mol) of sodium azide was added in portions during 4 hours, while maintaining a temperature of 65-70°. **Cautionary Note:** There can be a prolonged induction period before a considerable exotherm occurs which results in much foaming. Therefore, the temperature of the reaction should be carefully monitored and an ice-bath kept available for immediate cooling. After the addition was complete, the reaction was heated for an additional 16 hours at 60-65° at which time tlc (silica gel, diethyl ether) showed the absence of starting material. The solution was poured into 3.5 L of ice-water, the mixture was stirred for 1 hour, then extracted into dichloromethane (5 x 300 mL). The combined organic extracts were washed with water (5 x 300 mL) then saturated aqueous sodium carbonate (2 x 300 mL), dried, and concentrated to leave 32 g of an orange residue that was absorbed onto 200 mL of flash silica gel by dissolving it in 200 mL of dichloromethane, adding the silica gel, and then removing the dichloromethane under vacuum. The impregnated silica gel was applied to a column of 600 mL of silica gel and eluted with ether until **6** was no longer detected by tlc (silica gel, ether). Fractions containing **6** were pooled and concentrated to a residue that was crystallized from ethanol to give 2.8 g (8%) of **6** [9,10], mp 160-162° (lit [9] mp 160-161 °C) showing spectral data consistent with that reported in the literature [9]. ^{1}H NMR (DMSO-d_6): δ 10.02 (br s, exchanges with deuterium oxide, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 2.81 (t, J = 7.5 Hz, 2H), 2.42 (t, J = 7.5 Hz, 2H), 2.22 (s, 3H); EIMS *m/z* (relative %): 161 (M^+, 100); IR (KBR): 1684 cm^{-1}. Elution of the column with 9:1 ether:methanol gave fractions corresponding to **1**. These were pooled and concentrated to a residue that was crystallized from ethyl acetate:hexanes to afford 9.8 g (29%) of **1**, mp 108-110°. ^{1}H NMR (DMSO-d_6): δ 7.90 (br s, exchanges with deuterium oxide, 1H), 7.68 (s, 1H), 7.29 (d, J = 6.7 Hz, 1H), 7.21 (d, J = 6.7 Hz, 1H), 3.37 (td, J = 6.6 Hz, exchanges to t with deuterium oxide, 2H), 2.86 (t, J = 6.6 Hz, 2H), 2.34 (s, 3H); EIMS *m/z* (relative %): 161 (M^+, 82); 132 (100); IR (potassium bromide): 1660 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.12; H, 6.85; N, 8.65.

5-Methyl-1(2*H*)-isoquinolinone (**9**).

A mixture of 81.1 g (0.5 mol) of (*E*)-3-(2-methylphenyl)-2-propenoic acid (**8**) [5], 43.8 mL (0.6 mol) of thionyl chloride, and 400 mL of dichloromethane was heated at reflux for 1 hour. The solution was concentrated to a free-flowing oil that was further concentrated *in vacuo* overnight at 25° to remove remaining volatiles.

The light orange acid chloride was dissolved in 100 mL of *p*-dioxane and added dropwise over 1 hour to a 0° suspension of 97.5 g (1.5 mol) of sodium azide in 400 mL of 1:1 *p*-dioxane:water. During the addition the temperature was maintained at < 5°. After complete addition of the acid chloride, the mixture was stirred for 1 hour at 0°, then diluted with 375 mL of water. The mixture was then extracted with dichloromethane (3x), the combined extracts were dried, then concentrated at < 40° to 200-300 mL. The solution was diluted with 100 mL of diphenyl ether and further concentrated to remove the remaining dichloromethane. A 2 L 3-necked round bottom flask fitted with a nitrogen inlet, reflux condenser, and internal thermometer was charged with 143 mL of tributylamine and 400 mL of diphenyl ether. The solution was heated to 230° and the acyl azide in 100 mL of diphenyl ether was added dropwise over ~3 hours from an addition funnel. During the addition, the reflux temperature gradually decreased to 160°. Hence, after completion of the addition, the flask was fitted with a Dean-Stark trap, and distillate was collected and removed until the temperature reached 230° (~150 mL of a 1:1 mixture of tributylamine and diphenyl ether by gc). After heating for an additional hour, the mixture was cooled to 25°, then poured into 2.7 L of stirring petroleum ether. The precipitated solids were collected by filtration, washed with two 250 mL portions of petroleum ether, and air dried to leave 60.3 g of a yellow solid, mp 178-184°. The solid was slurried in ~275 mL of methanol, the suspension boiled for 30 minutes, then filtered and dried to leave 47 g (59%) of pure **9** as a pale yellow solid, mp 185-187° (lit [13,15] mp 184-185°), with spectral data identical to that described before [15]. The

methanol filtrate was concentrated to provide 15.8 g of additional impure product in two crops. These were combined and recrystallized from methanol to give 7.2 g (9%) of pure **9**, mp 183-187°.

3,4-Dihydro-5-methyl-1(2*H*)-isoquinolinone (**2**).

A mixture of 50 g (314 mmol) of isoquinolinone **9** in 500 mL of glacial acetic acid was hydrogenated at 50 psi over 2 g of 20% palladium on charcoal at 25° until the theoretical amount of hydrogen had been absorbed. The mixture was filtered and concentrated to a solid that was crystallized from 220 mL of 2-propanol to give 37.2 g (73%) of **2**, mp 139-141°, as white plates. The mother liquor was concentrated to afford an additional 10.9 g (22%) of **2** in two crops, mp 139-141°. ^{1}H NMR (deuteriochloroform): δ 7.95 (d, *J* = 7.4 Hz, 1H), 7.34-7.22 (m, 2H), 3.56 (t, *J* = 6.7 Hz, 2H), 2.92 (t, *J* = 6.7 Hz, 2H), 2.32 (s, 3H); IR (potassium bromide): 1658 cm^{-1}; EIMS *m/z* (relative %): 161 (M$^+$, 89), 132 (100).

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.46; H, 6.78; N, 8.62.

3,4-Dihydro-5-hydroxy-1(2*H*)-isoquinolinone (**11**).

A mixture of 50 g (310 mmol) of 1,5-dihydroxy-1(2*H*)-isoquinoline (**10**) in 1.6 L of glacial acetic acid and 5 g of 20% palladium on charcoal was hydrogenated at 50° until the theoretical amount of hydrogen had been absorbed. The solution was concentrated to a solid that was crystallized from water (600 mL) to give 43 g (85%) of **11** [18], mp 195.5-197°. ^{1}H NMR (DMSO-d_6): δ 9.80 (s, 1H), 7.83 (s, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 3.33 (m, 2H), 2.75 (t, *J* = 6.7 Hz, 2H); IR (potassium bromide): 3200, 1658, 1579, 790 cm^{-1}; EIMS *m/z* (relative %): 163 (M$^+$, 96), 51 (100).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.62; H, 5.46; N, 8.45.

3,4-Dihydro-5-(3-chloropropoxy)-1(2*H*)-isoquinolinone (**12**).

A mechanically stirred mixture of 40 g (245 mmol) of the dihydroisoquinolinone **11**, 88 g (637 mmol) of anhydrous potassium carbonate, and 1 L of absolute ethanol was heated under nitrogen at reflux. After 1 hour, 121 mL (1.22 mol) of 1-bromo-3-chloropropane was added dropwise over a 20 minute period. The mixture was refluxed for 2 hours, cooled to 60°, filtered, and the filtrate was concentrated to a white solid. The solid was dissolved in 375 mL of chloroform, and the solution was washed with water (3 x 125 mL), dried, and concentrated to a solid that was triturated in hot ethyl acetate. After cooling, the solid was collected by filtration and dried to give 50.6 g (86%) of **12**, mp 132-134°. ^{1}H NMR (deuteriochloroform): δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.30 (t,*J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.68 (s, 1H), 4.16 (t,*J* = 5.8 Hz, 6.4 Hz, 2H), 3.76 (t,*J* = 6.4 Hz, 2H), 3.55 (dt, *J* = 6.7 Hz, 2.8 Hz, 2.9 Hz, 2H), 2.97 (t, *J* = 6.7 Hz, 2H), 2.28 (q, *J* = 6.1 Hz, 2H); IR (potassium bromide): 1660, 1580 cm^{-1}; EIMS *m/z* (relative %): 253 (M$^+$, 22), 91 (100).

Anal. Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84; Cl, 14.79. Found: C, 59.95; H, 5.91; N, 5.80; Cl, 14.72.

3,4-Dihydro-5-[3-(methylamino)propoxy]-1-(2*H*)-isoquinolinone, Monohydrochloride (**3**).

A mixture of 25 g (104 mmol) of dihydroisoquinolinone **12**, 500 mL of 40% aqueous methylamine, and 550 mL of methanol was heated at 80° with stirring in a Parr pressure vessel for 21 hours. The cooled mixture was concentrated to an oily solid that was dissolved in 150 mL of water. The aqueous solution was washed with chloroform (2 x 150 mL), then concentrated to leave an off-white solid. The solid was dissolved in 500 mL of methanol/concentrated aqueous ammonia (20:1), then chromatographed over silica gel eluting with the same solvent mixture. Fractions containing pure product were combined then concentrated to leave 21 g of a solid, mp 110-111°. The solid was recrystallized from 400 mL of ethyl acetate to give 19.4 g (79%) of **3** as the free base, mp 112-113°. The material was dissolved in 300 mL of ethanol and 7.2 mL (86.4 mmol) of concentrated hydrochloric acid was added. The solution was concentrated to a solid that was recrystallized from a solution of 1.5 L 2-propanol and 150 mL water to afford 17.9 g (64%) of **3** as the hydrochloride salt, mp 259-260°. ^{1}H NMR (DMSO-d_6): δ 9.13 (br s, 2H), 7.95 (s, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.8, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 4.12 (t, *J* = 6 Hz, 2H), 3.49 -3.33 (m, 2H), 3.06 (m, 2H), 2.84 (t, *J* = 6.6 Hz, 2H), 2.55 (t, *J* = 5.4 Hz, 3H), 2.12 (qtp, *J* = 6.1, 7.3 Hz, 2H); IR (potassium bromide): 1663 cm^{-1}; EIMS *m/z* (relative %): 234 (M$^+$, 17), 44 (100).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$•HCl: C, 57.67; H, 7.07; N, 10.35; Cl$^-$, 13.09. Found: C, 57.30; H, 7.26; N, 9.97; Cl$^-$, 12.55.

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