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Facile and Convenient Syntheses of 6,11-Dihydro-5*H*-indeno[1,2-*c*]isoquinolin-5-ones and 6,11-Dihydro-5*H*-indolo[3,2-*c*]isoquinolin-5-one

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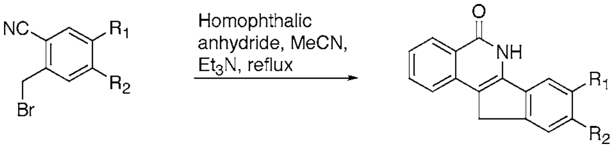
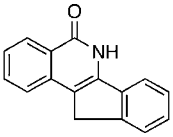
ABSTRACT



The synthesis of 6,11-dihydro-5*H*-indeno[1,2-*c*]isoquinolin-5-ones from the base-promoted condensation reaction of homophthalic anhydride and 2-(bromomethyl)-benzonitrile and a convenient method for the synthesis of indolo[3,2-*c*]isoquinolinones are described.

The therapeutic importance of poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors[1] has generated much interest in the discovery of new classes of heterocyclic PARP scaffolds. The structure−activity relationships (SAR) studies of these new heterocycles have identified several novel tri- and tetracyclic PARP-1 inhibitors.[2] The PARP-1 drug discovery that has been carried out during the past few years has led to various new approaches for the design of mainly cyclic benzamide inhibitors of the nuclear enzyme PARP-1.[2] There is continued interest in the discovery of new PARP-1 inhibitors, which is reflected by several recent publications and reviews.[2]

While searching for the new scaffolds that can be used for the SAR studies we aimed to synthesize new lactams whose modified derivatives would likely be inhibitors of PARP-1. The classes of recently synthesized PARP-1 inhibitors[2] that have displayed potent PARP-1 inhibitory activity are derived from the prototypical inhibitors, isoquinolin-1(2*H*)-one,[3] quinazolin-4(3*H*)-one,[3] and [5*H*]-phenanthridin-6-one.[3,4] The tetracyclic compounds indeno[1,2-*c*]-, indolo[3,2-*c*]-, and benzofuro[3,2-*c*]isoquinolinone (**1**−**3**) and their derivatives have never been evaluated for their PARP-1 activity. Thus, due to the structural similarity of indeno[1,2-*c*]-, indolo[3,2-*c*]-, and benzofuro[3,2-*c*]isoquinolinones (Figure 1) with the known inhibitors isoquinolin-1(2*H*)-one[3] and [5*H*]-phenanthridin-6-one,[3,4] these tetracycles appeared as attractive target molecules for synthesis and biological evaluation.



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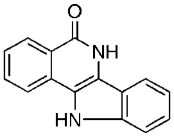

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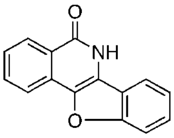

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Figure 1. Structures of indeno[1,2-*c*]-, indolo[3,2-*c*]-, and benzofuro[3,2-*c*]isoquinolinones (**1**−**3**).

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(1) Virag, L.; Szabó, C. *Pharmacol Rev.* **2002**, *54*, 375−429.

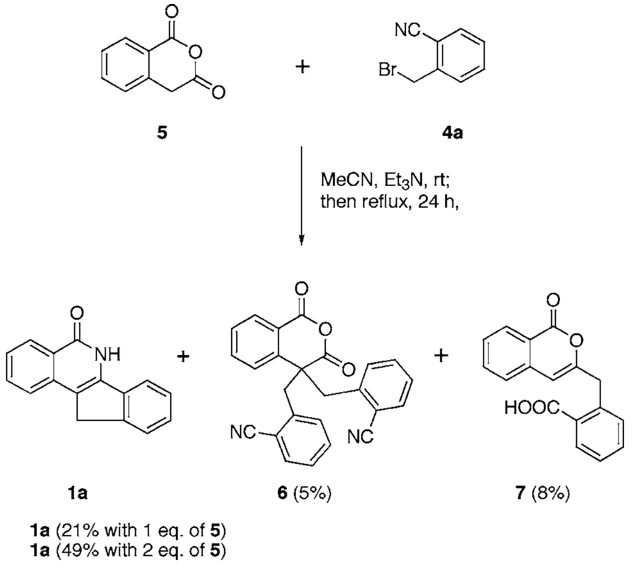
(2) (a) Jagtap, P.; Szabó, C. *Nat. Rev. Drug. Discovery* **2005** (in press). (b) Southan, G. J.; Szabó, C. *Curr. Med. Chem.* **2003**, *10*, 321−340. (c) Peukert, S.; Schwahn, U. *Expert Opin. Ther. Pat.* **2004**, *14*, 1531−1551.

10.1021/ol050331m CCC: $30.25

The only difference in the structures of the tetracycles **1**, **2**, and **3** is in the five-membered ring. There are a limited number of methods available for the synthesis of **1**,[5] **2**,[6] and **3**.[7] Cushman et al. have reported a series of indenoisoquinolinones starting from 11-keto tetracyclic lactone benz[*d*]indeno[1,2-*b*]pyran-5,11-dione.[5a] In this study, the indenoisoquinolinones were prepared by reacting the corresponding lactones with an amine followed by the reduction of the keto group using a diborane. Hiremath et al.[6] and Yamaguchi et al.[7] have reported the syntheses of indolo[3,2-*c*]isoquinolinone (**2**) and benzofuro[3,2-*c*]isoquinolinone (**3**), respectively. Previous synthesis of **2** involves multistep reactions starting from the 2-phenylindole.[6] Yamaguchi et al.[7] have described two synthetic pathways for the unsubstituted benzofuro[3,2-*c*]isoquinolinone **3** that involve the condensation reaction of diethyl-α-bromohomophthalate (**8**) with salicylonitrile (**9**) or methyl salicylate. The lack of commercial availability of the benz[*d*]indeno[1,2-*b*]pyran-5,11-dione and the low yielding synthesis of **2**[6] led us to develop alternative syntheses for the tetracycles **1** and **2**. Here, we report efficient synthetic approaches for **1** and **2** and a proposed mechanism for the formation of these compounds by using Yamaguchi's synthesis of **3**.

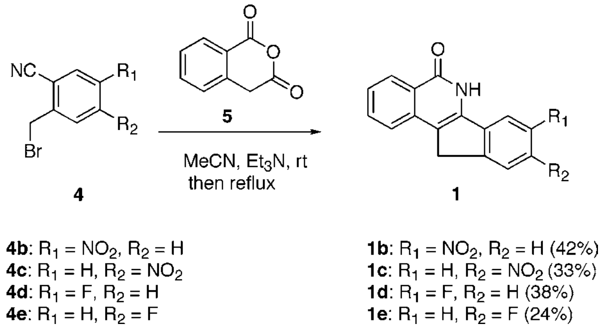
Our initial efforts to synthesize **1** and **2** by extending Yamaguchi's method[7] for the synthesis of **3** were unsuccessful. The condensation reactions were tried using various combinations of starting materials in the presence of a base: (1) reaction of diethyl α-bromohomophthalate[6] (**8a**) with 2-methylbenzonitrile, (2) reaction of diethyl homophthalate with 2-(bromomethyl)-benzonitrile (**4a**), (3) reaction of homophthalic acid with **4a**, and (4) reaction of **8a** with anthranilonitrile.

Scheme 1. Synthesis of Indeno[1,2-*c*]isoquinolinone **1a**



However, the reaction of homophthalic anhydride (**5**) and 2-(bromomethyl)benzonitrile (**4a**) in acetonitrile using triethylamine provided **1a** as the major product along with **6** and **7** (Scheme 1). The desired product **1a** was insoluble in acetonitrile, and it was easily isolated from other byproducts by filtration. Products **6** and **7** were separated from the filtrate by column chromatograph. This synthetic approach was further used for the synthesis of substituted indeno[1,2-c]isoquinolinones **1b**−**e**, which were obtained in 24−42% yield (Scheme 2).

Scheme 2. Synthesis of Indeno[1,2-*c*]isoquinolinones **1b**−**e**



Following Yamaguchi's method,[7] compound **3** was prepared by condensation of 2-cyanophenol (**9**) and bromodiester **8a**[7b] in acetone and in the presence of potassium carbonate. A similar condensation reaction using **8b** and **9** was also carried out using acetonitrile and triethylamine. Our initial efforts to prepare **2** from the condensation reaction of anthralinonitrile and **8b** in the presence of potassium carbonate were not successful. However, treatment of the *N*-ethyl carbamate derivative **10**[8a] with **8b** in the presence of sodium hydride[8b] in toluene provided the desired product **11** in 45% yield. Hydrazinolysis of **11** ($NH_2NH_2{\cdot}H_2O$, EtOH) yielded indolo[3,2-*c*]isoquinolinone (**2**)[6] in 88% yield (Scheme 3).

We were unable to isolate the conjugate acid of **13a** from the reaction of **5** and **4a** as shown in Scheme 5. The relative electrophilicity of benzonitrile and bezylbromide, using homophthalic anhydride as nucleophile, was studied by reacting a mixture of homophthalic anhydride (**5**), 3-nitrobenzyl bromide (**15**), and 4-nitrobenzonitrile (**16**) with a solution of triethylamine in acetonitrile at room temperature. The reaction was completed immediately after the addition of triethylamine. TLC analysis showed the consumption of

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(3) Banasik, M.; Komura, H.; Shimoyama, M.; Ueda, K. *J. Biol. Chem.* **1992**, *267*, 1569−1575.

(4) Garcia Soriano, F.; Virag, L.; Jagtap, P.; Szabó, E.; Mabley, J.; Liaudet, L.; Marton, A.; Hoyt, D. G.; Murthy, K. G.; Salzman, A. L.; Southan, G. J.; Szabó, C. *Nat. Med.* **2001**, *7*, 108−113.

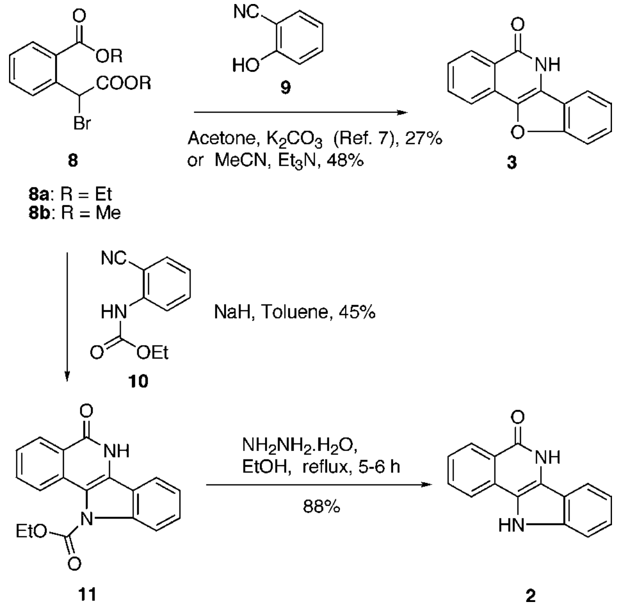
(5) (a) Cushman, M.; Jayaraman, M.; Vroman, J. A.; Fukunaga, A. K.; Fox, B. M.; Kohlhagen, G.; Strumberg, D.; Pommier, Y. *J. Med. Chem.* **2000**, *43*, 3688−3698. (b) Chatterjea, J. N.; Mukherjee, H. *J. Indian Chem. Soc.* **1960**, *37*, 379−391.

(6) (a) Hiremath, S. P.; Saundane, A. R.; Mruthyunjayaswamy, B. H. M. *Orient. J. Chem.* **1997**, *13*, 173−176. (b) Soundane, A. R.; Rudresh, K.; Satyanarayan, N. D.; Hiremath, S. P. *Indian J. Pharm. Sci.* **1998**, *60*, 379−383.

(7) (a) Yamaguchi, S.; Uchiuzoh, Y.; Sanada, K. *J. Heterocycl. Chem.* **1995**, *32*, 419−423. (b) Yamaguchi, S.; Yoshida, K.; Miyajima, I.; Araki, T.; Hirai, Y. *J. Heterocycl. Chem.* **1995**, *32*, 1517−1519.

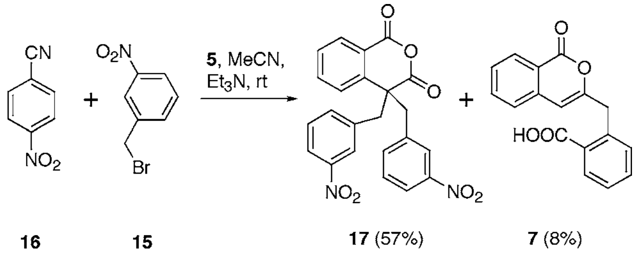
(8) (a) Radl, S.; Konvicka, P.; Vachal, P. *J. Heterocycl. Chem.* **2000**, *37*, 855−862. (b) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Heterocycl. Chem.* **1973**, *10*, 51−53.

Scheme 3. Synthesis of Indolo[3,2-*c*]- and Benzofuro[3,2-*c*]isoquinolinones



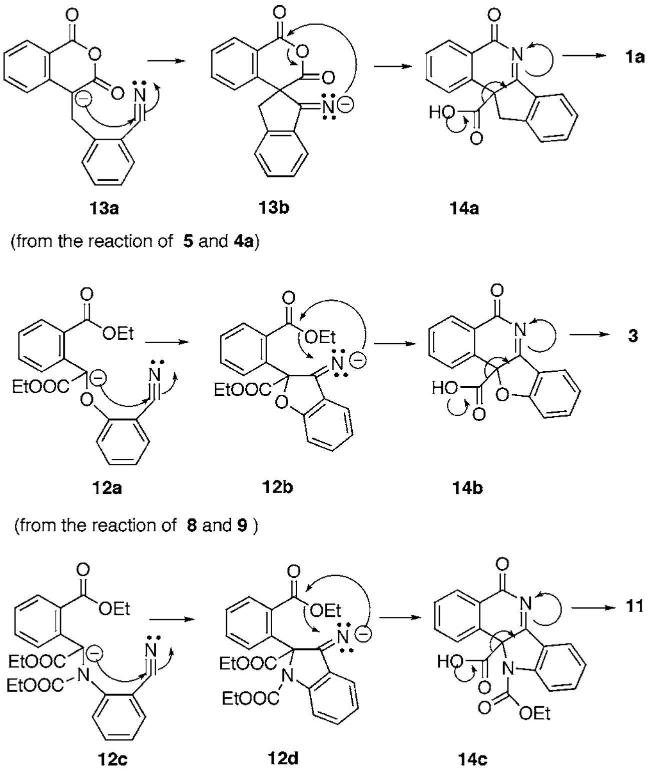
5 and 15, and after separation of the crude products, the α,α-di(3-nitrobenzyl)-homophthalic anhydride (**17**) appeared as the major product along with a minimal amount of homophthalic anhydride dimer **7**. The 4-nitrobenzonitrile remained unreactive under the above-mentioned reaction conditions. Although we were not able to isolate the intermediate **13a**, the formation of dibenzylated adducts **6** (Scheme 1) and **17** (Scheme 4) support the proposed mechanism, where intermediate **13a** may have formed from the reaction of homophthalic anhydride (**5**) and 2-(bromomethyl)benzonitrile (**4a**).

Scheme 4. Reaction of Homophthalic Anhydride with **15** and **16**



There is published evidence for the formation of the reactive benzylic enolate form of homophthalic anhydride. Earlier, homophthalic anhydride has been used for the synthesis of anthracyclinones[9] and isoquinolones.[10] The anthracyclinone precursors were prepared by strong base induced cycloaddition reaction of **5** with various dienophiles. The isoquinolinones were prepared by condensation of **5** with Schiff bases. The formation of the dimer **7** from the reaction of homophthalic anhydride with a base has been previously reported.[11] Here, we propose a mechanism for the formation of tetracyclic compounds **1** and **11** that is similar to the mechanism in the previous synthesis of **3**.[7] In all three cases, the initial reaction is the displacement of the bromine, which leads to the formation of the intermediates **13a**, **12a**, and **12c** (Scheme 5). The benzylic anion of diester (**12a** and **12c)** or anhydride (**13a)** then attacks to the nitrile group to form the intermediates **13b**, **12b**, and **12d** respectively. Further cyclization produces the intermediate **14**. In the case of diethyl homophthalate, the ester hydrolysis of **12b** and **12d** gives an intermediate **14**. Decarboxylation in intermediate **14** then produces the tetracyclic compounds **1a**, **3**, and **11**.

Scheme 5. Proposed Mechanism for the Formation of **1a**, **3**, and **11**



In conclusion, we have synthesized indeno[1,2-*c*] and indolo[3,2-*c*]isoquinolinones (**1** and **2**) by modifying Yamaguchi's synthesis of **3**. The current method provides an easy access to the synthesis of tetracyclic compound **1a**, using readily available reagents **5** and **4a**. In addition, these

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(9) Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1984**, *49*, 473−478.

(10) (a) Cushman, M.; Madaj, E. J. *J. Org. Chem.* **1987**, *52*, 907−915. (b) Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. *J. Org. Chem.* **2005**, *70*, 350−352.

(11) (a) Ayyangar, N. R.; Srinivasan, K. V. *Indian J. Chem.* **1983**, *22B*, 1108−1115. (b) Sinha, N. K.; Sahay, L. K.; Prasad, K.; Srivastava, J. N. *Indian J. Heterocycl. Chem.* **1992**, *1*, 235−240. (c) Bauta, W. E.; Lovett, D. P.; Cantrell, Jr., W. R.; Burke, B. D. *J. Org. Chem.* **2003**, *68*, 5967−5973.

processes opened route for the modification of the core structures **1** and **2**.[12] The reaction mechanisms were suggested by analogy with that in the synthesis of **3**. The SAR studies of this series of compounds are still underway. The in vitro and in vivo experimental results of our lead compound, which is based on scaffold **1** will be published elsewhere.

Acknowledgment. This work was supported by grants from the National Institutes of Health (R44DK054099 and R44GM058986).

Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for the new and known products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Jagtap, P.; Baloglu, E.; van Duzer, J. H.; Szabó, C.; Salzman, A.; Roy, A.; Williams, W.; Nivorozhkin, A. U.S. Patent Appl. 0039009A1, 2004.