Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

The Preparation of Substituted 1(2H)-Isoquinolinones from Polylithiated 2-(2-Methylphenyl)Hydrazinecarboxylic Acid Esters

Madlene U. Koller [a], Cameron A. Church [a], Cynthia L. Griffith [a], Margaret A. Hines [a], Rene J. Lachiocotte [a], Richard A. Taylor [a] & Charles F. Beam [a]

[a] Department of Chemistry and Biochemistry, College of Charleston, Charleston, South Carolina, 29424

Published online: 21 Aug 2006.

To cite this article: Madlene U. Koller, Cameron A. Church, Cynthia L. Griffith, Margaret A. Hines, Rene J. Lachiocotte, Richard A. Taylor & Charles F. Beam (1996) The Preparation of Substituted 1(2H)-Isoquinolinones from Polylithiated 2-(2-Methylphenyl)Hydrazinecarboxylic Acid Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:9, 1763-1774, DOI: 10.1080/00397919608002616

To link to this article: http://dx.doi.org/10.1080/00397919608002616

SYNTHETIC COMMUNICATIONS, 26(9), 1763-1774 (1996)

THE PREPARATION OF SUBSTITUTED 1(2H)-ISOQUINOLINONES FROM POLYLITHIATED 2-(2-METHYLPHENYL)HYDRAZINECARBOXYLIC ACID ESTERS

Madlene U. Koller, A. Cameron Church, Cynthia L. (Mazat) Griffith, Margaret A. Hines, Rene J. Lachicotte, Richard A. Taylor, and Charles F. Beam*

Department of Chemistry and Biochemistry
College of Charleston
Charleston, South Carolina 29424

ABSTRACT: 2-(2-Methylphenyl)hydrazinecarboxylic acid esters were metalated with excess lithium diisopropylamide, and the resulting polyanion-type intermediates were condensed with aromatic esters followed by acid cyclization to the 3-substituted-1(2H)-isoquinolinones (isocarbostyrils).

Our attention has been focused on several reports dealing with the metalation/condensation/cyclization of *ortho*-toluamides for the preparation of new and potentially useful products[1-3]. For example, the isolable δ-hydroxyamides [*e.g.*, 2-(2-hydroxy- 2,2-diphenylethyl)-benzanilide], made by condensing the dianion-type intermediates with ketones, were cyclized to what first appeared to be 4,5-dihydro-1(2H)-isoquinolinones[1b] (dihydroisocarbostyrils) but were later shown to be mainly 3,4-dihydro-1H-benzopyran-1-imines[4]. Our only earlier involvement with this project was with the readily reproducible preparation of δ-hydroxyamides and related materials[5]. Of special interest to this investigation was the metalation of N,2-dimethylbenzamide with *n*-butyllithium followed by condensation/

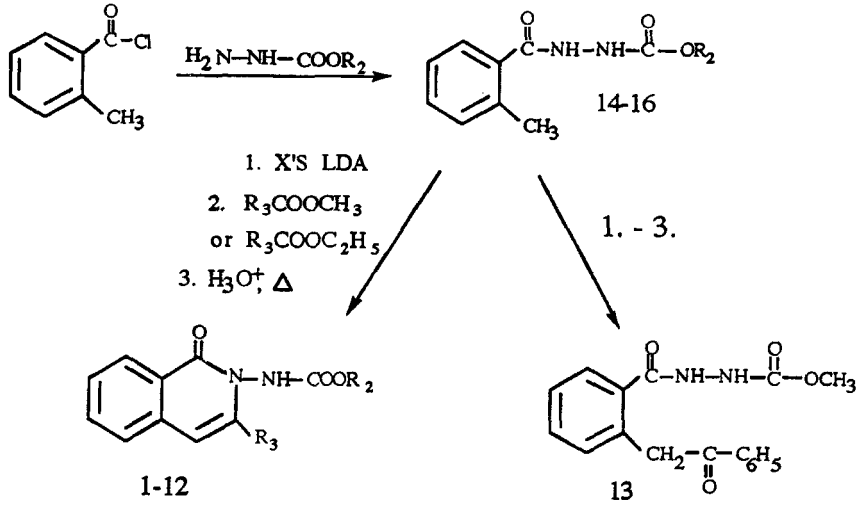
*To whom correspondence should be addressed.

cyclization with N,N-dimethylamides[3] to yield 1(2H)-isoquinolinones, which also have been prepared and extensively studied by others[6]. Reports concerning the treatment of 1H-2-benzopyran-1-ones (isocoumarins) with acetylhydrazine or hydrazine for the preparation of new 1(2H)-isoquinolinones with potential biological activity[7,8] have resulted in our continued studies concerning strong-base synthesis of similar 1(2H)-isoquinolinones **1-12** (Table).

Each of the entry compounds is new. Two of the 2-(2-methylphenyl)-hydrazinecarboxylic acid esters **15** (ethyl) and **16** (*t*-butyl)(bottom of Table) were prepared by the Schotten-Baumann condensation of *ortho*-toluoyl chloride with ethyl carbazate (for **15**) or *tert*-butyl carbazate[9] (for **16**). This technique did not work well for the condensation of the acid chloride with methyl carbazate. Compound **14** was prepared by the simple modification of another procedure[10] [1:1:1 - acid chloride:carbazate:pyridine]. The 2-(2-Methylphenyl)-hydrazine-carboxylic acid esters (**14-16**) were then metalated with excess lithium diisopropylamide (LDA) to presumed trianion-type intermediates[11] [subst. hydrazine:LDA:ester - 1:4:1 (for aromatic esters) or 1:5:1 (for phenolic esters)]. The polylithiated intermediates underwent a condensation with a variety of esters, followed by acid-cyclization to the 1(2H)-isoquinolinones **1-12** (Table). When a lesser amount of LDA was used for this procedure [subst. hydrazine:LDA:ester - 1:3:1], other products of minor interest were isolated instead[12].

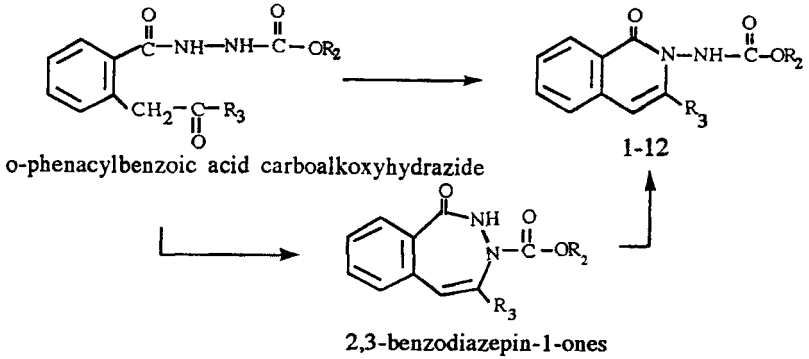
All of the 1(2H)-isoquinolinones, **1-12**, prepared by this strong-base procedure are new and were characterized by absorption spectra[13] [FT-IR, ^{1}H nmr] along with support from combustion analysis (for C, H, and N)[14]. The infrared spectra of the products displayed N-carboalkoxy absorptions from 1720 - 1749 cm^{-1}. The lactam-type carbonyl absorptions for each material were noted from 1638 - 1681 cm^{-1}. Proton nuclear magnetic resonance for each compound displayed a

distinctive vinyl absorption at C-4 (s), δ 6.44 - 6.55 ppm and aromatic absorptions were usually noted in two sets of distinct multiplets ranging between δ 6.70 - 7.88 and 8.13 - 8.65 ppm. Pendant group absorptions were noted for the ethoxy group in **1, 4, 5, 9** and **11** ranging between δ 4.10 - 4.16 ppm (q) for $-OCH_2-$ and 1.10 - 1.20 ppm (t) for CH_3-; for $-OC(CH_3)_3$ in **3, 6, 8, 10,** and **12** ranging between δ 1.35 - 1.42 ppm (s); for $-OCH_3$ in **2** and **7**, δ 3.70 - 3.72 ppm(s); for $ArCH_3$ in **4**, δ 2.38 ppm (s); for $ArOCH_3$ in **10**, δ 3.80 ppm (s); for $ArOCH_3$in **11** and **12** ranging between δ 3.88 - 3.92 ppm (s); and for $Ar-C(CH_3)_3$ in **5** and **7**, δ 1.33 and 1.37 ppm (s), respectively.



The yields of 1(2H)-isoquinolinones **1 - 12** ranged from 36-90%, which indicates that the general experimental procedure is usually satisfactory for the expedient preparation of 0.5-1.0 gram quantities of the desired products that can be purified by recrystallization from routine solvents. This may not necessarily represent the optimum conditions for the preparation of an individual compound. Acid hydrolysis of the carbo-*tert*-butoxy group did not occur in 1(2H)-iso-

quinolinones **3, 6, 8, 10,** and **12,** and this may indicate that the carboxy oxygen was not as readily protonated as initially expected. This is in contrast to previous projects, in which oxime and benzoylhydrazone functional groups in other molecules were readily hydrolyzed under similar conditions[15,16].



The C-acylated precyclization intermediate, *ortho*-phenacylbenzoic acid carbomethoxyhydrazide **13,** resulting from condensation of the polyanion-type intermediate (from **14**) with methyl benzoate was isolated. Usually these intermediates were acid cyclized directly to the heterocyclic products in a two-step single-pot reaction. The *ortho*-phenacylbenzoic acid carboalkoxyhydrazide intermediates may have the opportunity to undergo cyclodehydration to either the 1(2H)-isoquinolinone or the 2,3-benzodiazepin-1-one[7,17]. There is preference for the formation of the six-membered ring 1(2H)-isoquinolinone over the seven membered ring 2,3-benzodiazepin-1-one, and literature reports[7,8,17] indicated preferential formation of the 1(2H)-isoquinolinones. Under the acid cyclization conditions in this study, 2,3-benzodiazepin-1-ones if formed would have undergone rearrangement to the 1(2H)-isoquinolinones[17]. Specifically, isocoumarins were treated with acetylhydrazine or hydrazine[7,8] to give similar precyclization intermediates, *ortho*-phenacylbenzoic acid acetylhydrazides or

ortho-phenacylbenzoic acid hydrazides, that underwent cyclodehydration to the 1(2H)-isoquinolinones. *ortho*-Phenacylbenzoic acid carboalkoxyhydrazides are similar intermediates, and they underwent cyclization in an analogous manner to the 1(2H)-isoquinolinone. Related 2,3-benzodiazpin-1-ones are prepared by condensation of *ortho*-phenacylbenzoic acids with hydrazines[17a]. The position of the double bond (N-3, C-4) in the seven-membered ring for these compounds is different from 2,3-benzodiazepin-1-ones indicated as potential products (C-4, C-5) from cyclizations of the C-acylated intermediate precursors (*i.e.*, **13**) for compounds prepared during this investigation. Under acid conditions, these compounds also undergo rearrangement to 1(2H)-isoquinolinones[17k].

Several additional points are noted: [1] 1(2H)-Isoquinolinones **1 - 3** resulted from the condensation of polyanion-type intermediates with a lithiated hydroxybenzoate[11c], in which the phenoxide ion is in a position to diminish the electrophilicity of the carboethoxy carbon and therefore its reactivity towards a Claisen-type condensation. [2] The experimental procedure is straightforward so that someone not necessarily familiar with strong-base procedures can be successful with the reactions. [3] Since the synthesis is regioselective, and essentially a single product results, the final product is readily purified by simple recrystallization from routine solvents.

General Experimental Procedure for Preparation of 2-(2-Methylphenyl)hydrazine Carboxylic Acid Esters: The molar ratio of *o*-toluoyl chloride to hydrazinecarboxylic ester was 1:2[9,10]. Approximately 30 mL of 10% sodium hydroxide solution was added to 0.1 mol. of *tert*-butyl or ethyl carbazate, and enough ethanol was added to effect almost complete solution, *ca.* 10-30 mL (some turbidity). Then 0.05 mol of acid chloride was slowly added to the stirred solution (room temperature) at a slow dropwise rate. After the acid chloride was added, the

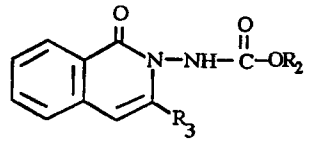


TABLE - 1(2H)-Isoquinolinones

Compd. No.	R_2	R_3	Molecular Formula[a,b]	%Yield/Mp[c] (°C)
1	C_2H_5	4-HOC_6H_4	$C_{18}H_{16}N_2O_4$	55/227-30[d]
2	CH_3	4-HOC_6H_4	$C_{17}H_{14}N_2O_4$	50/260-62[d]
3	$C(CH_3)_3$	4-HOC_6H_4	$C_{20}H_{20}N_2O_4$	90/249-52[d]
4	C_2H_5	4-$CH_3C_6H_4$	$C_{19}H_{18}N_2O_3$	76/158-60[d]
5	C_2H_5	4-$(CH_3)_3CC_6H_4$	$C_{22}H_{24}N_2O_3$	77/178-79[d]
6	$C(CH_3)_3$	C_6H_5	$C_{20}H_{20}N_2O_3$	48/185-86[d]
7	CH_3	4-$(CH_3)_3CC_6H_4$	$C_{21}H_{22}N_2O_3$	40/207-09[d]
8	$C(CH_3)_3$	3-ClC_6H_5	$C_{20}H_{19}ClN_2O_3$	45/158-59[d]
9	C_2H_5	4-ClC_6H_4	$C_{18}H_{15}ClN_2O_3$	36/174-75[d]
10	$C(CH_3)_3$	4-$CH_3OC_6H_4$	$C_{21}H_{22}N_2O_4$	70/212-13[e]
11	C_2H_5	3,4,5-$(CH_3O)_3C_6H_2$	$C_{21}H_{22}N_2O_6$	48/204-06[d]
12	$C(CH_3)_3$	3,4,5-$(CH_3O)_3C_6H_2$	$C_{23}H_{26}N_2O_6$	88/195-97[d]

[a]Combustion analysis data; ref. 14. [b]Spectral data; ref. 13. [c]Melting points were obtained with a Mel Temp melting point apparatus in open capillary tubes and are uncorrected. [d]Recryst. from ethanol or ethanol/water; see ref. 18. [e]Recryst. from ethanol/benzene.

Intermediate **13** resulting from condensation of polymetalated **14** with methyl benzoate; $C_{17}H_{16}N_2O_4$, mp 107-09° (55% - MeOH). Compds: **14**, 2-(2-methylphenyl)hydrazinecarboxylic acid, methyl ester, $C_{10}H_{12}N_2O_3$, mp 149-52° (44% - MeOH); **15**, 2-(2-methylphenyl)-hydrazinecarboxylic acid, ethyl ester $C_{11}H_{14}N_2O_3$, mp 149-52° (64% - EtOH); **16**, $C_{13}H_{18}N_2O_3$, 2-(2-methylphenyl)hydrazinecarboxylic acid, *t*-butyl ester, mp 124-26° (67% - MeOH).

mixture was stirred for several hours or stored overnight. It was then filtered through a Buchner funnel, washed with 50 mL of ice water, and dried. The products were recrystallized from either ethanol or methanol. The procedure for condensation of benzoyl chloride with alkyl carbazate was followed for the condensation of *o*-toluoyl chloride with methyl carbazate (1:1:1 - acid chloride:carbazate:pyridine). Reagent grade tetrahydrofuran (THF) was used instead of methylene chloride, which permitted the use of a magnetic stirrer in place of a mechanical stirrer[10b].

General Experimental Procedure for Preparation of 1(2H)-Isoquinolinones:

In a typical preparation, *n*-butyllithium[19] (0.079 mol. for condensation with ethyl 4-hydroxybenzoate for preparation of **1-3** or 0.063 mol. for preparation of **4-12**) was added to a three-necked round-bottomed flask (*ca.*, 500 mL) with a syringe. The flask was also fitted with a side-arm addition funnel (*ca.*, 125 mL) and nitrogen inlet tube. After cooling the flask in an ice water bath, a sample of diisopropylamine (0.079 mol. for **1-3** or 0.063 mol. for **4-12**) dissolved in 25 mL of dry THF (sodium - benzophenone/ketyl) was added to the stirred *n*-butyllithium at a fast dropwise rate (5-7 min.). The resulting LDA was stirred at 0° for an additional 20 min. before adding, during 5-7 min., a 0.015 mol. sample of 2-(2-methylphenyl)hydrazine carboxylic acid ester dissolved in 30-40 mL of dry THF.

The metalation time was 90 min. (0°, N_2), followed by condensation with a 0.0158 mol. sample of ester dissolved in 30-40 mL of dry THF, during 5 min. The condensation time varied (1-2 hr.) depending on the ester used (*e.g.*, methyl benzoate, 60 min.; methyl 3,4,5-trimethoxybenzoate, 75-90 min.; and methyl 4-hydroxybenzoate, 120 min.). If precipitation occurred, the ice bath was removed, and the mixture was stirred at room temperature.

Condensation was followed by neutralization and cyclodehydration. Acidification was accomplished by directly adding 100 mL of 3N hydrochloric acid, followed by heating the well stirred two-phased mixture under reflux for 30-45 min. At the end of the reflux period, the mixture was poured into a large flask (1L) containing ice (*ca.*, 100 gm.). This was followed by addition of 100 mL of solvent grade ether, and the resulting mixture was neutralized with sodium bicarbonate (pH paper to pH 4 for **1-3**), which was followed by separation of organic and aqueous phases. The aqueous layer was extracted with ether (2 x 75 mL), and the organic solutions were combined, dried ($MgSO_4$), filtered, and evaporated. The oil or solid residue was recrystallized from the solvent or mixture of solvents noted in the footnote of the Table.

ACKNOWLEDGMENTS: We wish to thank the Donors of the Petroleum Research Fund, administered by the American Chemical Society and the Research Corporation for support. Dr. Shannon Studer Martinez assisted with the preparation of the manuscript and was involved in numerous discussions.

REFERENCES AND NOTES:

1. (a) Vaulx R.L., Puterbaugh, W.H., and Hauser, C.R., *J. Org. Chem.*, **1964**, *29*, 3514. (b) Mao. C.-L., Barnish, I.T., and Hauser, C. R., *J. Heterocyclic Chem.*, **1969**, *6*, 83. (c) Watanabe, H., Mao, C.-L., and Hauser, C. R., *J. Org. Chem.*, **1969**, *34*, 1786. (d) Mao, C.-L., and Hauser, C.R., *J. Org. Chem.*, **1970**, *35*, 3704.
2. Wasserman, H.H., Lipshutz, K.H., *Tetrahedron Lett.*, **1975**, 1731.
3. Mali, R.S., Kuklarni, B.K., and Shankaran, K., *Synthesis*, **1982**, 329.
4. (a) Bailey, D.M., and DeGarzia, C.G., *J. Org. Chem.*, **1970**, *35*, 4088. (b) Bailey, D.M. and DeGarzia, *Tetrahedron Lett.*, **1970**, *9*, 633.
5. Beam, C.F., Park, C.A., Reames, D.C., Miller, S.J.A., and Hauser, C.R., *J. Chem. and Eng. Data.*, **1978**, *23*, 183.

6. (a) Pelletier, S.W., "Chemistry of Alkaloids", Van Nostrand Reinhold Co., New York, New York, 1970, p. 77; (b) Shamma, M., and Mionot, J.L., "Isoquinoline Alkaloid Research", Plenum Press, New York, New York, 1978, p. 51; (c) Iida, H., Kawano, K., Kikuchi, T., and Yoshimizu, *Yakuggaka Zasshi*, **1976**, *96*, 176. (d) Girling, I.R., and Widdowson, D.A., *J. Chem. Soc., Perkin Trans 1*, **1988**, 1317. (e) VanderGoot., H., and Nauta, W., Th., *Acta Pharm. Suecica*, **1971**, *8*, 373. (f) Izumi, T. and Marishita, N., *J. Heterocycl. Chem*, **1994**, *31*, 145. (g) Cobas, A., Guitian, E., and Castedo, L., *J. Org. Chem.*, **1993**, *58*, 3113. (h) Couture, A., Cornet, H., and Grandclaudon, P., *J. Organometal. Chem.*, **1992**, *440*, 7. (i) Couture, A. and Grandclaudon, P., *Tetrahedron*, **1992**, *49*, 3857. (j) Stanoeva, E., Haimova, M., and Ognyanov, V., *Liebigs Ann., Chem.*, **1984**, 389.

7. 2-Acylamino-3-phenyl-1(2H)-isoquinolinones: Ueno, S., Sugihara, K., Hirayama, H., and Ichino, M., *Japan Kokai*, **1976**, 76,122,075; *Chem. Abstr.*, **1977**, *87*, 5822a.

8. 2-Amino-1(2H)-isoquinolinones: (a) Huisgen, R. and Rauenbusch, E., *Ann.*, **1961**, *641*, 51. (b) Boyers, J.T. and Glover, E.E., *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1960. (c) Datta. D., and Usgaonkae, *Indian J. Chem.*, **1981**, *20B*, 376. (d) Gurevich, A.I., Kolasov, M.N., Omelchenko, V.N., Onoprienko,V.V., and Petrenko, G.I., *Bioorg. Khim.*, **1975**, *1*, 166. (e) Legrand, L. and Lozac'h, *Bull. Soc. Chem. Fr.*, **1970**, 2240.

9. Only the ethyl 2-(3-methylphenyl)hydrazinecarboxylate and 2-(4-methylphenyl)hydrazinecrboxylate isomers have been reported. See: Grekov, A.P. and Veselov, V. A., *Zh. Org. Khim.*, **1971**, *7*, 323; *Chem. Abstr.*, **1971**, *75*, 48108s.

10. (a) We found Schotten-Baumann condensation procedures of aromatic carboxylic acid chlorides too general. In order to avoid excess diacylation and still be able to make the entry compound expediently, we used a procedure that gave the desired entry compounds in 50 - 70% yield. (b) See also: Carpino, L.A., Terry, P.H., and Crowley, P.J., *J. Org. Chem.*, **1961**, *26*, 4336.

11. (a) Fulmer, T.D., Dasher, L.P., Bobb, B.L., Wilson, J.D., Sides, K.L., and Beam, C.F., *J. Heterocycl. Chem.*, **1980**, *17*, 799. (b) Huff, A.M., Hall, H.L., Smith, M.J., O'Grady, S.A., Waters, F.C., Fengl, R.W., Welch, J.A., and Beam, C.F., *J. Heterocycl. Chem.*, **1985**, *22*, 501. (c) Duncan, D. C.,

Trumbo, T.A., Almquist, C.D., Lentz, T.A., and Beam, C.F., *J. Heterocycl. Chem.*, **1987**, *24*, 555.

12. We noted the following resonance absortions for these products, which were not starting materials: ^{1}H nmr ($CDCl_3$), δ 2.47 and 2.60 ppm ($ArCH_3$). The spectra indicated that metalation of the *ortho* methyl hydrogens had not occurred.
13. Infrared spectra were obtained from a Mattson Polaris FT-Infrared Spectrometer. ^{1}H nmr were obtained from a Varian Associates, EM-360L Nuclear Magnetic Resonance Spectrometer, and chemical shifts are reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. [Compound No. from Table, ir (paraffin oil), cm^{-1}; nmr (solvent);] Compd. **1**; ir, 3379 (OH), 3313 (NH), 1721 (C=O), and 1646 (N-C=O); nmr (DMSO-d_6) δ 1.17 (t, CH_3), 4.11 (q, -OCH_2-), 6.68 (s, C_4-H), 6.77 - 7.88 and 8.20 - 8.43 (m, ArH), and 10.30 (s, broad, ArOH). Compd. **2**; ir, 3426 (OH), 3239 (NH), 1722 (C=O), and 1653 (N-C=O); nmr (DMSO-d_6) δ 3.68 (s, OCH_3), 6.63 (s, C_4-H), and 6.78 - 7.88 and 8.13 - 8.45 (m, ArH). Compd. **3**; ir, 3354 (OH), 3212 (NH), 1745 (C=O), and 1638 (Ar and N-C=O); nmr (DMSO-d_6/ $CDCl_3$), δ 1.40 (s, -$OC(CH_3)_3$), 6.48 (s, C_4-H), 6.70-8.55 (m, ArH). Compd. **4**; ir, 3179 (NH), 1749 (C=O), 1648 (Ar and N-C=O); nmr ($CDCl_3$) δ 1.10 (t, CH_3-), 2.38 (s, $ArCH_3$), 4.10 (q, -OCH_2-), 6.50 (s, C_4-H), 7.13 - 7.73 and 8.30 - 8.53 (m, ArH). Compd. **5**; ir, 3250 (NH), 1720 (C=O), and 1681 (Ar and N-C=O); nmr ($CDCl_3$) δ 1.15 (t, CH_3-), 1.33 (s, Ar-$C(CH_3)_3$), 4.16 (q, -OCH_2-), 6.52 (s, C_4-H), and 7.25 - 7.77 and 8.33 - 8.58 (m, ArH). Compd. **6**; ir, 3180 (NH), 1746 (C=O), 1652 (Ar and N-C=O); nmr ($CDCl_3$) δ 1.38 (s, -$OC(CH_3)_3$), 6.53 (s, C_4-H), and 7.22 - 7.88 and 8.35 - 8.65 (m, ArH). Compd. **7**; ir, 3265 (NH), 1726 (C=O), and 1687 (Ar and N-C=O); nmr ($CDCl_3$) δ 1.37 (s, $ArC(CH_3)_3$), 6.55 (s, C_4-H), 3.72 (s, OCH_3), and 7.28 - 7.88 and 8.33 - 8.63 (m, ArH). Compd. **8**; ir, 3174 (NH), 1747 (C=O), and 1648 (Ar and N-C=O); nmr ($CDCl_3$) δ 1.42 (s, -$OC(CH_3)_3$), 6.52 (s, C_4-H), and 7.23 - 7.78 and 8.40 - 8.63 (m, ArH). Compd. **9**; ir, 3218 (NH), 1744 (C=O), and 1668 (Ar and N-C=O); nmr ($CDCl_3$) δ 1.13 (t, CH_3-), 4.14 (q, -OCH_2-), 6.52 (s, C_4-H), and 7.33 - 7.87 and 8.33 - 8.55 (m ArH). Compd. **10**; ir, 3171 (NH), 1742 (C=O), 1643 (Ar and N-C=O); nmr (DMSO-d_6) δ 1.35 (s, -$OC(CH_3)_3$), 3.80 (s, -OCH_3), 6.63 (s, C_4-H), and 6.90 - 7.88 and 8.13 - 8.45 (m, ArH). Compd. **11**; ir, 3176

(NH), 1749 (C=O), 1653 (Ar and N-C=O); nmr ($CDCl_3$) δ 1.20 (t, CH_3-), 4.16 (q, -OCH_2-), 3.88 and 3.92 (s, $ArOCH_3$), 6.53 (s, C_4-H), and 7.43 - 7.87 and 8.30 - 8.63 (m, ArH). Compd. **12**; ir, 3288 (NH), 1745 (C=O), and 1670 (N-C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.42 (s, -$OC(CH_3)_3$), 3.88 and 3.90 (s, $ArOCH_3$), 6.53 (s, C_4-H), and 6.77 - 7.80 and 8.37 - 8.57 (m, ArH). Compd. **13**; ir, 3178 (NH), 1726 (C=O), and 1681 (Ar and N-C=O); nmr ($CDCl_3$) δ 3.70 (s, OCH_3), 6.55 (s-br, CH=C, enol), and 7.17 - 7.77 and 8.37 - 8.57 (m, ArH). Compd. **14**; ir, 3242 broad (NH), 1737 (C=O-O), and 1662 cm^{-1} (C=O-N and Ar); nmr (DMSO-d_6) δ 2.28 (s, $ArCH_3$), 3.65 (s, -OCH_3), and 7.18 - 7.55 (m, ArH). Compd. **15**; ir, 3321 and 3233 (NH), 1732 (C=O-O), and 1663 (C=O-N and Ar); nmr ($CDCl_3$/DMSO-d_6) δ 1.25 (t, -CH_3), 2.42 (s, $ArCH_3$), 4.16 (q, -OCH_2-), and 7.13 - 7.68 (m, ArH). Compd **16**; ir, 3330 and 3244 (NH), 1722 (C=O-O), and 1660 (C=O-N and Ar); nmr ($CDCl_3$) δ 1.43 (s, -$OC(CH_3)_3$), 2.43 (s, ArH) and 7.12 - 7.68 (m, ArH).

14. Microanalysis for C, H, and N were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888 and Robertsons Laboratory, 8 Samson Avenue, Madison, NJ 07940. [Compd. No. from Table] Calcd. for **1**: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.90; H, 5.13; N, 8.37. Calcd. for **2**: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.74; H, 4.80; N, 8.74. Calcd. for **3**: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.16; H, 5.79; N, 7.96 Calcd. for **4**: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.49; H, 5.65; N, 8.65. Calcd. for **5**: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.54; H, 6.50; N, 7.69. Calcd. for **6**: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.40; H, 6.05; H, 8.25. Calcd. for **7**: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.04; H, 6.47; N, 7.88. Calcd. for **8**: C, 64.78; H, 5.16; N, 7.55. Found: C, 664.93; H, 5.13; N, 7.58. Calcd. for **9**: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.15; H, 4.55; N, 8.07. Calcd. for **10**: C, 68.84; H, 6.05; N, 7.64. Found: C, 68.88; H, 6.09; N, 7.56. Calcd. for **11**: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.22; H, 5.74; N, 6.88. Calcd. for **12**: C, 64.78; H, 6.14; N, 6.57. Found: C, 64.69; H, 6.21; N, 6.66. Calcd. for **13**: C, 65.38; H, 5.16; N, 8.96. Found: C, 65.34; H, 5.28; N, 8.85. Calcd. for **14**: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.77; H, 5.86; N, 13.49. Calcd. for **15**: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.38; H, 6.44; N, 12.46. Calcd. for **16**: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.43; H, 6.99; N, 11.19.

15. Brown, J., Sides, K.L., Fulmer, T.D., and Beam, C.F., *J. Heterocycl. Chem.*, **1979**, *16*, 1669.

16. Mack, H.M., Davis, E.A., Kadkhodayan, B., Taylor, R.A., Duncan, D.C., and Beam, C.F., *J. Heterocycl. Chem.*, **1987**, *24*, 1733.

17. There are numerous reports concerning the preparation of 2,3-benzodiazepin-1-ones, and in each case the double bond is between N-3 and C-4, and not between C-4 and C-5. The latter location of the double bond would be in the 2,3-benzodiazepin-1-ones, if formed during the cyclization, prior to rearrangement to the 1(2H)-isoquinolinone (a) Ames, D.A., and Dodds, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 705; (b) Wolbling, H., *Ber.*, **1905**, *38*, 3846. (c) Wolbling, H., *Ber.*, **1905**, 2845. (d) Flammang, M., *C.R. Hebd. Seances Acad. Sci. Ser. C*, **1978**, *286*, 671; *Chem. Abstr.*, **1978**, *89*, 146878b. (e) Flammang, M., and Wermuth, C.G., *Eur. J. Med. Chem.-Chim. Ther.*, **1977**, *12*, 121. (f) Flammang, M. and Wermuth, C.G., *C.R. Hebd. Seances Acad. Sci. Ser. C*, **1980**, *290*, 361; *Chem. Abstr.*, **1980**, *93*, 203556d. (g) Rose, A., and Buu-Hoi, N.P., *J. Chem. Soc.*, **1968**, *C*, 2205. (h) Vorozhtov, N.N., and Petuchkova, A.T., *J. Gen Chem. USSR (Engl. Trans.)*, **1957**, *27*, 2342. (i) Somei, M., Karasawa, Y., Shoda, T., and Kaneko, C., *Chem. Pharm. Bull., Japan.*, **1981**, *29*, 249. (j) Grogan, F., O'Brian, A.E., Philbin, E.M., O'Conner, N.S., Tommoney, R.F., and Wheeler, T.S., *Tetrahedron*, **1958**, *3*, 140. (k) Legrand, L. and Lozac'h, N., *Bull. Soc. Chim. Fr.*, **1970**, 2237 and 2240.

18. Initially 95% ethanol was used. If crystals did not form in several hours or overnight (refrigerator), a few drops of water or a few ice crystals were added.

19. A 1.6 M solution in hexanes was obtained from Aldrich Chemical Co. This material is satisfactory enough to effect metalation and dilute enough to permit expedient and safe handling.

(Received in the USA 24 October 1995)