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

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Published online: 08 Jan 2009.

To cite this article: F. A. Amer, M. Hammouda, A. A. S. El-Ahl & B. F. Abdel-Wahab (2009) 3-Pyrrolidinones: Michael Addition and Schmidt Rearrangement Reactions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:3, 416-425, DOI: 10.1080/00397910802378373

To link to this article: http://dx.doi.org/10.1080/00397910802378373

Synthetic Communications®, 39: 416–425, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802378373

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3-Pyrrolidinones: Michael Addition and Schmidt Rearrangement Reactions

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Abstract: Various spiro-pyrano[3,2-b]pyrrolo-2-oxoindolines **3a–d** and dicyano-pyrano[3,2-b]pyrroles **5a–e** have been synthesized in the present study by Michael addition of 3-pyrrolidinones **1** to isatin-3-ylidenes **2** and arylidenemalononitrile **4**. Hexahydro-4-oxo-1-aryl-pyrimidine-5-carboxylic acids **7a,b** were synthesized from **1** by Schmidt rearrangement.

Keywords: Arylidenemalononitriles, isatin-3-ylidines, Michael addition, 3-pyrrolidinones, Schmidt rearrangement

INTRODUCTION

3-Pyrrolidinones are the key starting materials for the synthesis of a number of fused heterocycles, such as anticancer drugs (e.g., methotrexate),[1,2] floroquinolone antibacterials (e.g., gemifloxacin, norfloxacin),[3–6] and inhibitors of HIV-1 replication,[7] and DNA.[8,9] The medicinal applications of spiro-2-oxoindolines as muscle relaxants and anti-inflammatory agents is well known.[10,11] Several spiro-2-oxoindoline derivatives were reported to exhibit analgesics,[12] platelet aggregation inhibitory,[13] bactericidal, and central nervous system (CNS) depressant

Received January 2, 2008.

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activities.[14] The starting material, 3-pyrrolidinones **1a,b**, was prepared from primary aromatic amines, acrylonitrile, and ethyl bromoacetate according to the reported procedures.[15] In view of these observations and in continuation of our work on 3-pyrrolidinone,[16] the synthesis of novel spiro-pyrrolo[3,2-b]-4-pyranyl-2-oxoindoline, dicyanopyrrolo[3,2-b]-4-pyrane, and hexahydropyrimidin-4-one derivatives starting from N-aryl-3-pyrrolidinones by Michael addition and Schmidt rearrangement was studied.

RESULTS AND DISCUSSION

Michael Addition Reactions

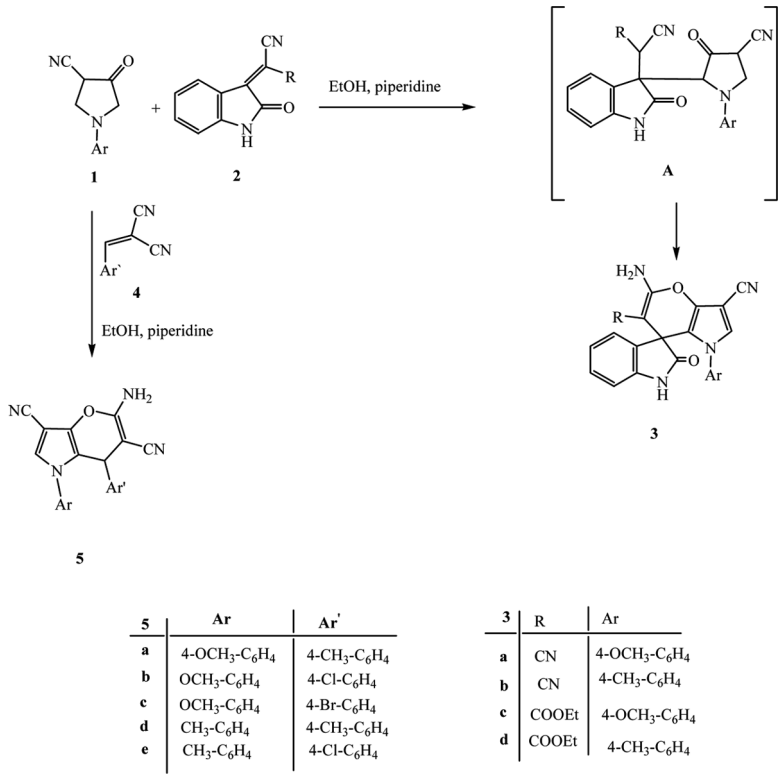
Base-catalyzed Michael addition of **1a,b** to the exocyclic double bond of the 3-ylidene derivative **2a,b** afforded the regiospecifically Michael adduct intermediate **A**, which underwent subsequent cyclization to give spiro-2-oxoindoline derivatives **3a–d** in good yield (Scheme 1). IR spectra of **3a** displayed an absorption band at 1708 cm^{-1} attributable for the carbonyl group of 2-oxoindoline part of the product, sharp absorption bands at 2235 and 2196 cm^{-1} for two carbonitrile groups.

The IR spectra of **3c** showed absorption bands at 1716 and 1678 cm^{-1}, which indicated the presence of two carbonyl groups, namely, the 2-oxoindoline carbonyl group and the carbethoxy carbonyl group. The IR spectra showed only one carbonitrile group at 2238 cm^{-1}. The ^1H NMR of **3c** showed four singlets at 9.7, 8.1, 7.51, and 3.76 ppm for NH, NH_2, pyrrole proton, and methoxy group, respectively, and also showed a quartet at 3.64 and a triplet at 0.69 ppm for CH_2 and CH_3 of carbethoxy group, respectively.

Treatment of **1a,b** with arylidenemalononitrile **4a–e** derivatives in ethanol containing a catalytic amount of piperidine afforded the pyrano-[3,2-b]pyrrole derivatives **5a–e** in good yields, which are oxoisosters of the corresponding indole derivatives and were expected to exhibit a wide spectrum of biological activity (Scheme 1).

The structure of pyrano[3,2-b]pyrroles **5a–e** is based on spectral and analytical data. The mass spectrum of **5b** showed the molecular ion peak at m/z 403, which is assigned to $M^+ + 1$. The ^1H NMR of **5a** revealed the presence of two protons as a broad singlet at 6.98 ppm, assigned for the amino group, and a sharp singlet at 7.68 ppm, assigned for the pyrrole ring proton.

One-pot synthesis of compound **5c** was investigated. Thus, when a mixture of **1a**, *p*-bromobenzaldehyde, and malononitrile in a molar ratio of 1:1:1 was refluxed in ethanol containing a catalytic amount of piperidine, the pyrano[3,2-b]pyrrole **5c** was isolated in a low yield. The reaction



5	Ar	Ar'
a	4-OCH_3-C_6H_4	4-CH_3-C_6H_4
b	OCH_3-C_6H_4	4-Cl-C_6H_4
c	OCH_3-C_6H_4	4-Br-C_6H_4
d	CH_3-C_6H_4	4-CH_3-C_6H_4
e	CH_3-C_6H_4	4-Cl-C_6H_4

3	R	Ar
a	CN	4-OCH_3-C_6H_4
b	CN	4-CH_3-C_6H_4
c	COOEt	4-OCH_3-C_6H_4
d	COOEt	4-CH_3-C_6H_4

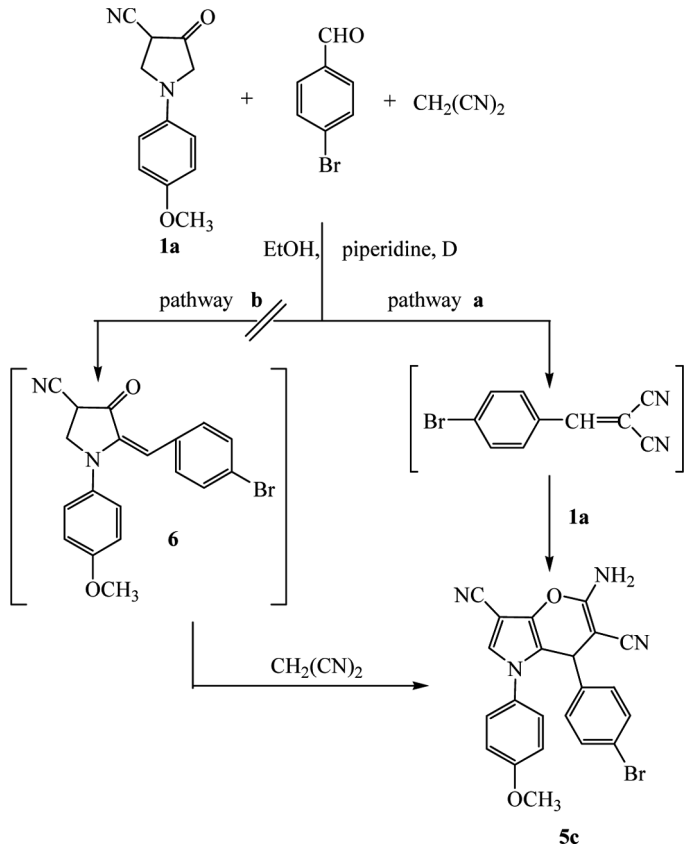
Scheme 1. Michael addition reaction.

could proceed via two pathways. In pathway a, the *p*-bromobenzaldehyde reacted first with malononitrile to give *p*-bromobenzylidenemalononitrile **2**, which reacted with 3-pyrrolidinone **1a** to give **5c**. In pathway b, the aldehyde reacted first with 3-pyrrolidinone to give *p*-bromobenzylidene-3-pyrrolidinone **6**, which underwent Michael addition reaction with malononitrile to give **5c** (Scheme 2).

To prove that the reaction could proceed through pathway a or b, we tried to prepare compound **6** by reaction of *p*-bromobenzaldehyde with **1a** in ethanol containing a catalytic amount of piperdine: the reaction did not proceed to afford *p*-bromobenzylidene derivative **6**.

Schmidt Rearrangement

3-Pyrrolidinones **1a,b** undergo Schmidt rearrangement conditions to afford hexahydropyrimidinones **7a,b** or 6-oxo-4-p-(substitutedphenyl)-piperazine-2-carboxylic acid **8a,b**. The Schmidt rearrangement was

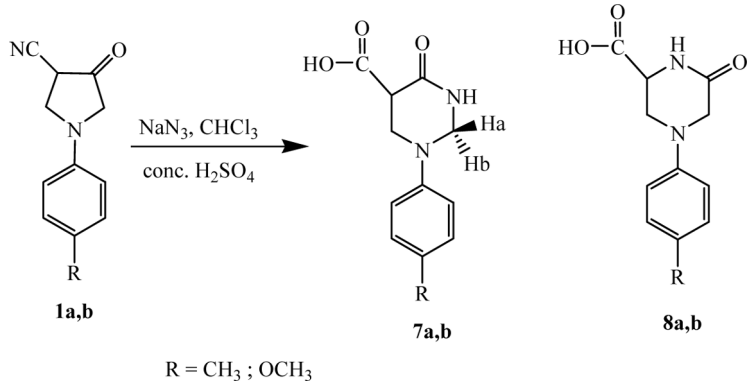


Scheme 2. One-pot synthesis of **5c**.

accompanied by hydrolysis of the cyano group into the carboxylic group (Scheme 3).

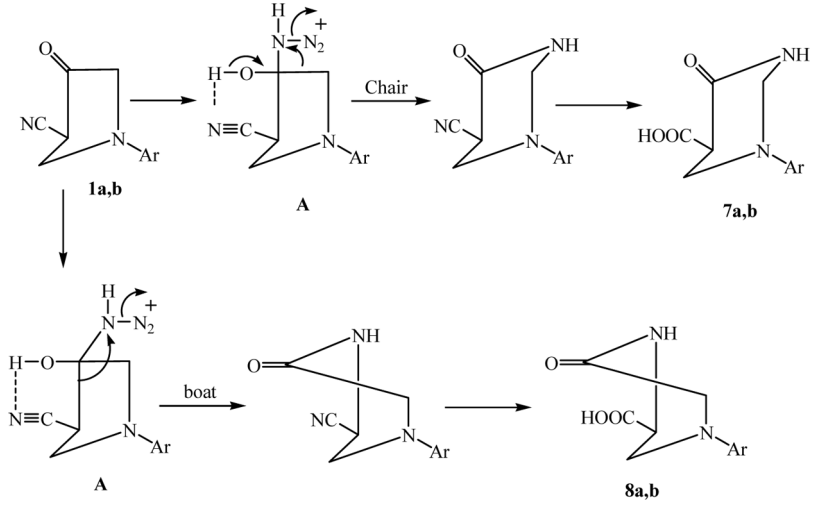
The structures of the hexahydropyrimidine derivatives **7a,b** were based on spectral and analytical data. The mass spectrum of **7b** displayed the molecular ion peak at m/z 248, which is assigned to $M^+ - 2$, and the major fragmentations were in agreement with the assigned structure.

^{1}H NMR confirmed the assigned structures of **7a,b** and excluded the structures **8a,b**. The ^{1}H NMR of **7b** displayed a doublet of doublet at 3.74–3.65 ppm, assigned for the magnetically nonequivalent protons Ha and Hb. The mechanism for the regiospecific rearrangement of **1a,b** shown in Scheme 4 was based upon the relative boat–chair conformations of strain energy. Synchronous rearrangement of azidohydrine with loss of nitrogen can lead directly to the lactam. Two possible



Scheme 3. Schmidt rearrangement reaction.

azidohydrines are derivable from 3-pyrrolidinones **1a,b**. If azide is primarily on the less hindered convex face of the molecule as in A, it would be stabilized by hydrogen bonding between the cyano and hydroxyl groups. Migration occurs with an energetically favored chair conformation, in which the azalactam **7a,b** will result via methylene migration. Methine migration of the same azidohydrine to afford **8a,b** would occur via the less favorable boat transition state.[17]



Scheme 4. Mechanism of Schmidt rearrangement.

EXPERIMENTAL

All melting points were taken on an Electrothermal IA 9000 series digital melting-point apparatus. Elemental analytical data (in accordance with the calculated values) were obtained from the Microanalytical Unit, Cairo University, Cairo, Egypt. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H NMR spectra were recorded at 270 MHz on a Varian EM-360 spectrometer using TMS as an internal standard. The mass spectra were performed using a Varian MAT CH-5 spectrometer (70 eV). All reactions were followed by thin-layer chromatography (TLC, silica gel, aluminum sheets 60 F^{254}, Merck). Physical data are given in Table 1.

Table 1. Physical data, yields, and elemental analysis for compounds **3**, **5**, and **7**

Cpd. no.	Molecular formula	Found, (%) [calculated (%)]			Mp (°C)	Yield (%)	Color
		C	H	N			
3a	$C_{23}H_{15}N_5O_3$	67.52 [67.47]	3.62 [3.69]	16.97 [17.11]	271–272	62	Pale yellow
3b	$C_{23}H_{15}N_5O_2$	70.32 [70.22]	3.77 [3.84]	17.65 [17.8]	258–259	62	Pale yellow
3c	$C_{25}H_{20}N_4O_5$	65.68 [65.78]	4.33 [4.42]	12.38 [12.27]	273–274	81	White
3d	$C_{25}H_{20}N_4O_4$	68.08 [68.17]	4.56 [4.58]	12.66 [12.72]	282–283	83	White
5a	$C_{23}H_{18}N_4O_2$	72.32 [72.24]	4.81 [4.74]	14.55 [14.65]	255–256	86	Pale yellow
5b	$C_{22}H_{15}ClN_4O_2$	65.44 [65.59]	3.85 [3.75]	13.94 [13.91]	260–262	77	Pale yellow
5c	$C_{22}H_{15}BrN_4O_2$	59.16 [59.07]	3.32 [3.38]	12.62 [12.53]	257–258	82	Pale yellow
5d	$C_{23}H_{18}N_4O$	75.02 [75.39]	4.71 [4.95]	15.18 [15.29]	198–200	69	Pale yellow
5e	$C_{22}H_{15}BrN_4O$	61.18 [61.26]	3.6 [3.51]	12.86 [12.99]	209–210	81	Pale yellow
7a	$C_{12}H_{12}N_2O_3$	62.06 [62.12]	5.21 [5.26]	12.06 [12.11]	186–187	82	Colorless
7b	$C_{12}H_{12}N_2O_4$	58.06 [58.11]	4.87 [4.89]	11.29 [11.32]	177–178	84	Colorless

Synthesis of Spiro-pyrano[3,2-b]pyrrole-2-oxoindoline Derivatives (3a–d)

A mixture of **1a** or **1b** (2 mmol) in ethanol (20 ml), compound **2** (0.4 g, 2 mmol in the case **3a,b** or 0.5 g, 2 mmol in the case **3c**,**d**), and two drops of piperidine were refluxed for 4 h, and left to cool overnight. The resulting solid product was filtered off and recrystallized from ethanol.

5-Amino-2-oxo-1-(4′-methoxyphenyl)-1,1′,2′,3a,7,7a′-hexahydrospiro[indole-3′,7-pyrano[3,2-b]pyrrole]-3,6′-dicarbonitrile (3a)

^{1}H NMR (DMSO-d_6): 3.68 (s, 3H, OCH_3), 6.30–6.91 (m, 8H, Ar-H), 7.31 (s, 1H, pyrrole-H), 7.64 (s, 2H, NH_2), 10.08 (s, 1H, NH). IR: 1708 cm^{-1}, 2196 cm^{-1}, 2235 cm^{-1}, 3381 cm^{-1}, 3319 cm^{-1}. Mass spectra: m/z 409 $[M]^+$.

5-Amino-2-oxo-1-(4′-methylphenyl)-1,1′,2′,3a,7,7a′-hexahydrospiro[indole-3′,7-pyrano[3,2-b]pyrrole]-3,6′-dicarbonitrile (3b)

^{1}H NMR (DMSO-d_6): 2.32 (s, 3H, CH_3), 6.24–6.88 (m, 8H, Ar-H), 7.36 (s, 1H, pyrrole-H), 7.98 (s, 2H, NH_2), 10.03 (s, 1H, NH). IR: 1706 cm^{-1}, 2196 cm^{-1}; 2234 cm^{-1}, 3301 cm^{-1}, 3278 cm^{-1}. Mass spectra: m/z 393 $[M]^+$.

Ethyl 5-Amino-3-cyano-2-oxo-1-(4′-methoxyphenyl)-1,1′,2′,3a,7,7a′-hexahydrospiro[indole-3′,7-pyrano[3,2-b]pyrrole]-6′-carboxylate (3c)

^{1}H NMR (DMSO-d_6): 0.69 (t, 3H, O-$CH_2\underline{CH_3}$), 3.64 (q, 2H, $O\underline{CH_2}CH_3$), 3.76 (s, 3H, OCH_3), 6.16–6.86 (m, 8H, Ar-H), 7.51 (s, 1H, pyrrole-H), 8.1 (s, 2H, NH_2), 9.7 (s, 1H, NH). IR: 1680 cm^{-1}, 1706 cm^{-1}, 2231 cm^{-1}, 3393 cm^{-1}, 3287 cm^{-1}. Mass spectra: m/z 456 $[M]^+$.

Ethyl 5-Amino-3-cyano-2-oxo-1-(4′-methylphenyl)-1,1′,2′,3a,7,7a′-hexahydrospiro[indole-3′,7-pyrano[3,2-b]pyrrole]-6′-carboxylate (3d)

^{1}H NMR (DMSO-d_6): 0.71 (t, 3H, O-$CH_2\underline{CH_3}$), 2.29 (s, 3H, CH_3), 3.58 (q, 2H, $OCH_2\underline{CH_3}$), 6.22–6.87 (m, 8H, Ar-H), 7.49 (s, 1H, pyrrole-H), 8.08 (s, 2H, NH_2), 9.6 (s, 1H, NH). IR: 1678 cm^{-1}, 1716 cm^{-1}, 2238 cm^{-1}, 3349, 3269 cm^{-1}. Mass spectra: m/z 440 $[M]^+$.

3.3.5-Amino-1,7-dihydro-1-(aryl)-7-(aryl)pyrano[3,2-b]pyrrole-3,6-dicarbonitrile (5a–e)

A mixture of **1a** or **1b** (2 mmol) in ethanol (20 ml), appropriate arylidene malononitrile **4** (2 mmol), and a few drops of piperidine were refluxed for 4 h and Left to cool. The resulting solid product was filtered off, dried, and recrystallized from ethanol.

5-Amino-1,7-dihydro-1-(4-methoxyphenyl)-7-p-tolylpyrano[3,2-b]pyrrole-3,6-dicarbonitrile (5a)

^{1}H NMR ($CDCl_3$): 2.2 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 4.8 (s, 1H, C_4-H), 6.59 (d, 4H, Ar-H), 6.98 (s, 2H, NH_2), 7.10–7.08 (d, 4H, Ar-H), 7.68 (s, 1H, C_6-H). IR: 2195 cm^{-1}, 2234 cm^{-1}, 3424 cm^{-1}, 3325 cm^{-1}. Mass spectra: m/z 382 $[M]^+$.

5-Amino-7-(4-chlorophenyl)-1,7-dihydro-1-(4-methoxyphenyl)pyrano[3,2-b]pyrrole-3,6-dicarbonitrile (5b)

^{1}H NMR ($CDCl_3$): 3.74 (s, 3H, OCH_3), 4.91 (s, 1H, C_4-H); 6.74 (d, 2H, $J = 8.38$, Ar-H), 6.86 (d, 2H; $J = 8.97$, Ar-H), 7.06–7.16 (m, 6H, 4Ar-H & NH_2), 7.71 (s, 1H, C_6-H). IR: 2195 cm^{-1}, 2235 cm^{-1}, 3418 cm^{-1}, 3324 cm^{-1}. Mass spectra: m/z 403 $[M+1]^+$, 402 $[M]^+$.

5-Amino-7-(4-bromophenyl)-1,7-dihydro-1-(4-methoxyphenyl)pyrano[3,2-b]pyrrole-3,6-dicarbonitrile (5c)

^{1}H NMR ($CDCl_3$): 3.68 (s, 3H, OCH_3), 4.91 (s, 1H, C_4-H), 6.72 (d, 2H, $J = 8.28$, Ar-H), 6.88 (d, 2H; $J = 8.97$, Ar-H), 7.17–7.09 (m, 6H, 4Ar-H & NH_2), 7.73 (s, 1H, C_6-H). IR: 2195 cm^{-1}, 2234 cm^{-1}, 3410 cm^{-1}, 3321 cm^{-1}. Mass spectra: m/z 448 $[M+2]^+$, 447 $[M+1]^+$, 446 $[M]^+$.

5-Amino-1,7-dihydro-1,7-dip-tolylpyrano[3,2-b]pyrrole-3,6-dicarbonitrile (5d)

^{1}H NMR ($CDCl_3$): 2.19 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.78 (s, 1H, C_4-H), 6.49 (d, 2H, Ar-H), 6.96 (s, 2H, NH_2), 7.07–7.18 (d, 2H, Ar-H), 7.69 (s, 1H, C_6-H). IR: 2195 cm^{-1}; 2238 cm^{-1}; 3369 cm^{-1}, 3319 cm^{-1}. Mass spectra: m/z 366 $[M]^+$.

5-Amino-7-(4-chlorophenyl)-1,7-dihydro-1-p-tolylpyrano-[3,2-b]pyrrole-3,6-dicarbonitrile (5e)

^{1}H NMR ($CDCl_3$): 2.14 (s, 3H, CH_3), 4.87 (s, 1H, C_4-H), 6.72 (d, 2H, $J = 8.35$, Ar-H), 6.87 (d, 2H; $J = 8.65$, Ar-H), 7.07–7.18 (m, 6H, 4Ar-H & NH_2), 7.68 (s, 1H, C_6-H). IR: 2206 cm^{-1}; 2238 cm^{-1}; 3330 cm^{-1}, 3280 cm^{-1}. Mass spectra: m/z 387 $[M + 1]^+$; 386 $[M]^+$.

Synthesis of 1-Aryl-5-carboxy-hexahydropyrimidin-4-ones 7a,b

To a stirred mixture of **1a** or **1b** (5 mmol) in chloroform (20 ml) and conc. sulfuric acid (4–5 ml) in an ice bath, sodium azide (0.325 g, 5 mmol) was added over a period of 1 h. The reaction mixture was stirred at room temperature for 4 h, then heated at 50–60 °C for 30 min. The reaction mixture was poured into ice-cold water and neutralized with ammonium hydroxide. The resulting solid product was filtered off, dried, and recrystallized from ethyl acetate to give **7a,b** as colorless crystals.

Hexahydro-4-oxo-1-p-tolylpyrimidine-5-carboxylic Acid (7a)

^{1}H NMR ($CDCl_3$): 2.29 (s, 3H, CH_3), 3.74–3.65 (dd, 2H, $J =$ 10 and 18 Hz, Ha & Hb at C_2), 4.08–3.92 (m, 3H, C_5-H & C_6-H_2), 5.66 (s, 1H, NH), 6.65 (d, 2H, $J = 8$ Hz, Ar-H), 6.85 (s, 1H, COOH), 7.12 (d, 2H, $J =$ 8 Hz, Ar-H). IR: 1669 cm^{-1}, 1763 cm^{-1} , 3203 cm^{-1}, 3405 cm^{-1}. Mass spectra: m/z 332 $[M - 2]^+$.

Hexahydro-1-(4-methoxyphenyl)-4-oxopyrimidine-5-carboxylic Acid (7b)

^{1}H NMR ($CDCl_3$): 3.51 (s, 3H, OCH_3), 3.74–3.65 (dd, 2H, $J =$ 10 and 18 Hz, Ha & Hb at C_2), 4.07–3.90 (m, 3H, C_5-H & C_6-H_2), 5.67 (s, 1H, NH), 6.61 (d, 2H, $J = 8$ Hz, Ar-H), 6.87 (s, 1H, COOH), 7.10 (d, 2H, $J =$ 8 Hz, Ar-H). IR: 1669 cm^{-1}, 1763 cm^{-1}, 3200 cm^{-1}, 3406 cm^{-1}. Mass spectra: m/z 248 $[M - 2]^+$.

REFERENCES

1. Taylor, E. C.; Fletcher, S. T.; Cody, V.; Kempton, R. J. Synthesis of acylpyrroles via α-(dimethy1amino)-α-pyrrolylacetonitriles. *J. Org. Chem.* **1988**, *53*, 6118.
2. Taylor, E. C.; Ahmed, Z.; Robke, D. J.; Kempton, R. J. Alternative syntheses of N-[4′-(alkoxycarbonylphenyl)]-3-pyrrolidinones. *J. Org. Chem.* **1991**, *56*, 5443.

3. Kim, B. C.; Kim, Y. D.; Choi, H.; Kim, W. S. A process for the preparation of pyrrolidino-quinoline-carboxylic acid derivatives (e.g., gemifloxacin with improved filtration). Patent PCT Int. Appl. WO 01 68,649, 2001; *Chem. Abstr.* 135, 242153a (2001).
4. Hong, C. Y.; Kim, Y. K.; Chang, J. H.; Kim, S. H.; Choi, H.; Nam, D. H.; Kim, Y. Z.; Kwak, J. H. Novel fluoroquinolone antibacterial agents containing oxime-substituted(aminoethyl)pyrrolidines: Synthesis and antibacterial activity of 7-(4-aminoethyl)-3-(methoxyimino)pyrrolidin-1-yl)-1-cyclopropyl-6-fluro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid. *J. Med. Chem.* **1997**, *40*, 3584.
5. Halazy, S.; Schwarz, M.; Quattropani, A.; Thomas, R.; Baxter, A.; Scheer, A. Synthesis of substituted N-acyl/sulfonyl pyrrolidine as bax inhibitors. Patent PCT Int. Appl. WO 01 72,705, 2001; *Chem. Abstr.* 135, 288686e (2001).
6. Lee, D. C.; Kwon, Y.; Kim, Y.; Rhee, C. High-yield process for preparing 3-aminomethyl-4-Z-methoxyiminopyrrolidine. Patent PCT Int. Appl. WO 02 18, 336, 2002; *Chem. Abstr.* 136, 216642k (2002).
7. Bouygues, M.; Medou. M.; Chermann, J. C.; Camplo, M.; Kraus, J. L. Short and unexpectedly potent 3-pyrrolidinone type inhibitors of HIV-1 replication. *Eur. J. Med. Chem.* **1998**, *33*, 445.
8. Kumar, R.; Lown, W. J. Design and synthesis of novel DNA interstrand cross-linking agents: C2-linked pyrrolo[2,1-c][1,4]benzodiazepine polyamide conjugates. *Heterocycl. Commun.* **2002**, *8*, 115.
9. Kamal, A.; Srinivas, O.; Ramulu, P.; Ramesh, G.; Kumar, P. P.; Kumar, M. S. Synthesis and DNA binding affinity of novel A-C8/C-C2-exo unsaturated alkoxyamido-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers. *Bioorg. Med. Chem.* **2004**, *12*, 4337.
10. Ninomyia, K. Spirolactone compounds. Japan Patent 80 164,683, 1980; *Chem. Abstr. 95*, 25036r (1982).
11. Kobayashi, G.; Matsuda, Y. Indole derivatives having spiro ring. Japan Patent 70 25,894, 1970; *Chem. Abstr. 74*, 3529t (1972).
12. Kobayashi, G.; Matsuda, Y. Pyrazoline derivatives as analgesics. Japan Patent, 68 03,385, 1968; *Chem. Abstr. 69*, 96716m (1969).
13. Kikugawa, K.; Ichino, M. Platelet aggregation inhibitors V: Pyrimidine derivatives, indole derivatives, benzothiophenes, and benzoquinolizine, derivatives. *Chem. Pharm. Bull.* **1973**, *21*, 1151.
14. Diebold, J. L.; Wolf, M. Spiro[2H, 3,1-1-benzooxazine]derivatives. U.S. Patent 3,711,476, 1973; *Chem. Abstr. 78*, 97672s (1974).
15. Su, T. L.; Watanabe, K. A. Chemistry of the pyrrolo[3,4-c]pyrido[2,3-d]pyrimidine system: Synthesis of 6,7-dihdropyrrolo[3,4-c]pyrido[2,3-d] pyrimidines, a novel ring system with potential biological interest. *J. Org. Chem.* **1989**, *54*, 220.
16. Amer, F. A.; Hammouda, M.; El-Ahl, A. A. S.; Abdel-Wahab, B. F. Synthesis of important new pyrrolo[3,4-c]pyrazoles and pyrazololyl-pyrrolines from heterocyclic β-ketonitriles. *J. Chin. Chem. Soc.* **2007**, *54*, 1543.
17. Krow, G. R. Nitrogen insertion reactions of bridged bicyclic ketones: Regioselective lactam formation. *Tetrahedron* **1981**, *37*, 1283.