A New Synthesis of Pyrimido[6,1-*a*]isoquinoline Derivatives and Related Compounds

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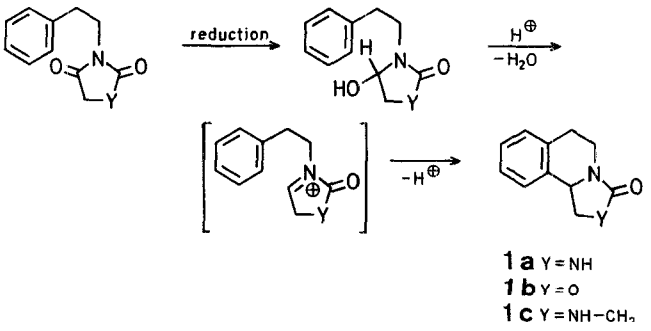
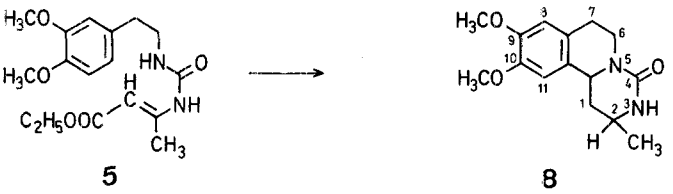
π-Cyclizations of several kinds of *N*-acyliminium ions have been used for the synthesis of a wide variety of heterocyclic systems[1]. Recently, derivatives of imidazoisoquinoline (**1a**)[2], oxazoloisoquinoline (**1b**)[3,4], and pyrazinoisoquinoline (**1c**)[5] and its thiophene isostere[6] were prepared by this method.



Heterocycles fused with pyrimidine and quinazoline rings are of interest from a pharmacological point of view[7] and many of their derivatives are useful drugs.

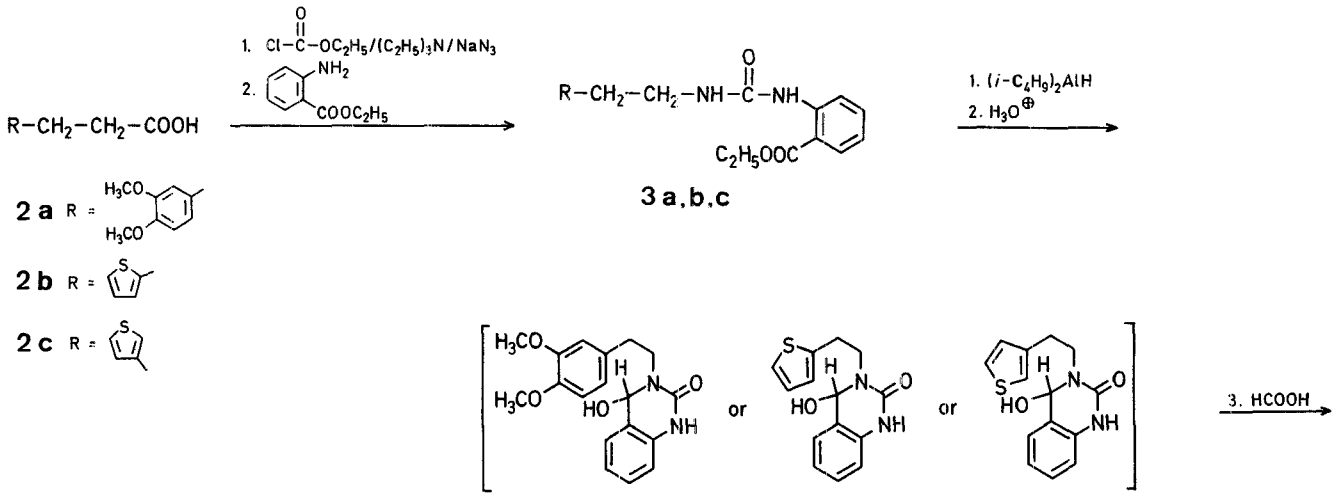
Our interest in new syntheses of pyrimidoisoquinolines and related compounds led us to develop the π-cyclization of α-heterosubstituted acyliminium ions to a synthesis of pyrimido[6,1-*a*]isoquinoline derivatives and related compounds starting with carboxylic acids[4].

The urea derivative **3a**, the precursor of the *N*-acyliminium ion which undergoes cyclization to **6a**, is easily obtained from 3-(3,4-dimethoxyphenyl)-propanoic acid (**2a**) via conversion into the acid azide followed by reaction with ethyl 2-aminobenzoate. In the same manner, acids **2b**[8] and **2c**[9] are converted into the urea derivatives **3b** and **3c**, respectively. Reduction of compounds **3a, b, c** with diisobutylaluminum hydride in toluene at −78 °C, followed by cyclization of the reduction products, without previous purification, with formic acid at room temperature affords the heterocyclic-fused quinazoline derivatives **6a, b, c**.



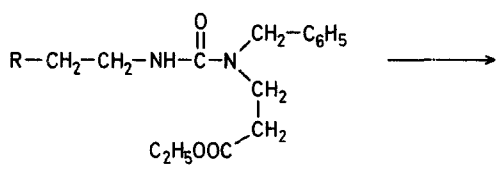
5 **8**

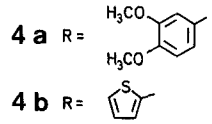
***N*-(2-Ethoxycarbonylphenyl)-*N'*-[-2-(3,4-dimethoxyphenyl)-ethyl]-urea (3a); Typical Procedure for Urea Derivatives 3, 4, and 5:**
Ethyl carbonochloridate (2.27 g, 21 mmol) is added dropwise, with ice cooling, to a stirred solution of 3-(3,4-dimethoxyphenyl)-propanoic acid (**2a**; 4.205 g, 20 mmol) and triethylamine (4.04 g, 40 mmol) in acetone (30 ml). After 20 min, a solution of sodium azide (1.95 g, 30 mmol) in water (2 ml) is added and stirring is continued for 15 min with ice cooling and for 1.5 h at room temperature. The mixture is then diluted with water (100 ml) and extracted with chloroform (300 ml). The extract is dried with sodium sulfate and evaporated to a volume of 30 ml. A mixture of this solution and ethyl 2-aminobenzoate (3.47 g, 21 mmol) is heated under reflux for 14 h. The solvent is then evaporated and the residue extracted with benzene (3 × 50 ml). The extract is washed with 5% hydrochloric acid

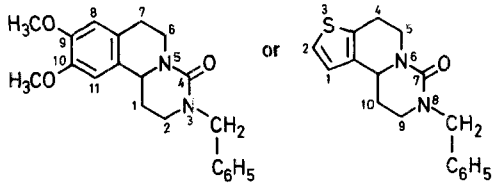


3a,b,c

In a similar manner, the urea derivatives **4a, b** (obtained from acids **2a, b** and ethyl 3-benzylaminopropanoate) are cyclized to the ring-fused pyrimidine derivatives **7a, b**.

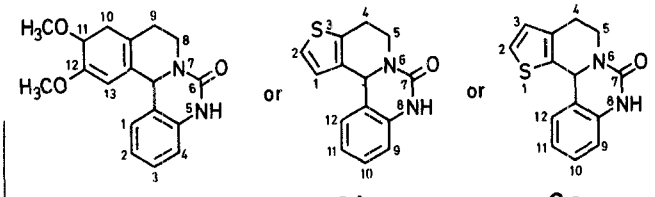






7a **7b**

In the case of urea derivative **5** (obtained from acid **2a** and ethyl 3-aminocrotonate), the olefinic double bond is reduced during the reaction so that the cyclization product **8** is obtained as a 1:1 mixture of diastereoisomers.



6a **6b** **6c**

(50 ml) and water (100 ml) and is dried with sodium sulfate. Removal of the solvent affords **3a** as a solid; yield: 5.80 g (78%); m.p. 114–115 °C.

$C_{20}H_{24}N_2O_5$	calc.	C 64.50	H 6.50	N 7.52
(372.4)	found	64.26	6.45	7.45

Cyclization Products 6, 7, and 8; General Procedure:
To a stirred solution of the urea derivative **3, 4**, or **5** (15 mmol) in toluene (50 ml) is added diisobutylaluminum hydride (4.26 g, 20.3 ml of 25% toluene solution) at −78 °C. Stirring is continued for 50 min at −78 °C and the mixture then decomposed with 5% sulfuric acid (70 ml) and extracted with chloroform (300 ml). The extract is dried with sodium sulfate and evaporated; the residue is used for the cyclization reaction without purification. A mixture of this residue and formic acid (10 ml) is stirred at room temperature for 14 h. The mixture is then basified with 28% ammonia and extracted with chloroform (2 × 100 ml). The extract is washed with water (100 ml), dried with sodium sulfate, and evaporated. The residue is chromatographed on silica gel (30 g). Elution with benzene (70 ml) and then with chloroform (30 ml) gives the starting urea and

Table 1. Urea Derivatives **3**, **4**, and **5** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula	M.S. *m/e* (M^+)	^{1}H.N.M.R. ($CDCl_3$/TMS_{int}) δ[ppm]
3a	78	114–115°	$C_{20}H_{24}N_2O_5$ (372.4)	372	1.40 (t, 3H, J = 7.5 Hz); 2.82 (t, 2H, J = 7 Hz); 3.43–3.65 (m, 2H), 3.88 (s, 6H); 4.31 (t, 2H, J = 7.5 Hz); 6.84 (br. s, 3H); 7.01 (t, 1H, J = 8 Hz); 7.56 (d, t, 1H, J = 2 and 8 Hz); 8.07 (d, d, 1H, J = 2 and 8 Hz); 8.63 (d, 1H, J = 8 Hz)
3b	75	oil	$C_{16}H_{18}N_2O_3S$ (318.4)	318	1.49 (t, 3H, J = 7.5 Hz); 3.10 (t, 2H, J = 7.5 Hz); 3.47–3.61 (m, 2H); 4.33 (q, 2H, J = 7.5 Hz); 6.89–7.22 (m, 4H); 7.52 (d, t, 1H, J = 2 and 8.5 Hz); 8.03 (d, d, 1H, J = 2 and 8.5 Hz); 8.59 (d, J = 8.5 Hz)
3c	72	oil	$C_{16}H_{18}N_2O_3S$ (318.4)	318	1.40 (t, 3H, J = 7.5 Hz); 2.93 (t, 2H, J = 7.5 Hz); 3.46–3.68 (m, 2H); 4.37 (q, 2H, J = 7.5 Hz); 6.98–7.44 (m, 4H); 7.54 (d, t, 1H, J = 2 and 8.5 Hz); 8.04 (d, d, 1H, J = 2 and 8.5 Hz); 8.58 (d, 1H, J = 8.5 Hz)
4a	84	oil	$C_{22}H_{30}N_2O_5$ (402.5)	402	1.24 (t, 3H, J = 7.5 Hz); 2.51 (t, 2H, J = 7 Hz); 2.73 (t, 2H, J = 7 Hz); 3.34–3.61 (m, 4H); 3.84 (s, 3H); 3.86 (s, 3H); 4.12 (q, 2H, J = 7.5 Hz); 4.47 (s, 2H); 6.74 (br. s. 3H); 7.14–7.41 (m, 5H)
4b	80	oil	$C_{19}H_{24}N_2O_3S$ (360.5)	360	1.51 (t, 3H, J = 7.5 Hz); 2.53 (t, 2H, J = 7 Hz); 3.02 (t, 2H, J = 7 Hz); 3.40–3.63 (m, 4H); 4.11 (q, 2H, J = 7.5 Hz); 4.48 (s, 2H); 6.79–7.01 (m, 2H); 7.14–7.39 (m, 6H)
5	67	oil	$C_{17}H_{24}N_2O_5$ (236.4)	236	1.26 (t, 3H, J = 7.5 Hz); 2.38 (s, 3H); 2.78 (t, 2H, J = 7 Hz); 3.36–3.59 (m, 2H); 3.88 (s, 6H); 4.14 (q, 2H, J = 7.5 Hz); 4.81 (s, 1H); 6.73–6.78 (m, 3H)

Table 2. Heterocyclic Compounds **6**, **7**, and **8** prepared

Product		Yield [%]	m.p. [°C]	Molecular Formula	M.S. *m/e* (M^+)	^{1}H.N.R. ($CDCl_3$/DMSO-d_6/TMS_{int}) δ[ppm]
6a	11,12-dimethoxy-6-oxo-5,6,8,9,10,11-hexahydro-13b*H*-isoquino[2,1-*c*]quinazoline	63	214–216°	$C_{18}H_{18}N_2O_3$[a] (310.3)	310	3.07–3.30 (m, 3H); 3.72 (s, 3H); 3.87 (s, 3H); 4.46–4.66 (m, 1H); 5.58 (br. s, 1H); 6.60 (s, 1H); 6.73 (s, 1H); 6.83–7.28 (m, 4H)
6b	7-oxo-4,5,7,8-tetrahydro-12b*H*-thieno[3′,2′:3,4]pyrido-[1,2-*c*]quinazoline	65	237–238°	$C_{14}H_{12}N_2OS$[a] (256.3)	256	2.60–2.93 (m, 1H); 2.99–3.31 (m, 2H); 4.47–4.69 (m, 1H); 5.69 (s, 1H); 6.71 (d, 1H, J = 5 Hz); 7.17 (d, 1H, J = 5 Hz); 6.83–7.45 (m, 4H)
6c	7-oxo-4,5,7,8-tetrahydro-12b*H*-thieno[2′,3′:3,4]pyrido-[1,2-*c*]quinazoline	60	245–246°	$C_{14}H_{12}N_2OS$[a] (256.3)	256	2.67–3.33 (m, 3H); 4.49–4.63 (m, 1H); 5.97 (s, 1H); 6.87 (d, 1H, J = 5 Hz); 7.01–7.45 (m, 4H); 7.23 (d, 1H, J = 5 Hz)
7a	3-benzyl-9,10-dimethoxy-4-oxo-1,2,3,4,6,7-hexahydro-11a*H*-pyrimido[6,1-*a*]isoquinoline	72	oil	$C_{21}H_{24}N_2O_3$ (352.4)	352[b]	1.89–3.43 (m, 7H); 3.84 (s, 3H); 3.87 (s, 3H); 4.43–4.90 (m, 4H); 4.64 (s, 1H); 6.68 (s, 1H); 7.43 (s, 5H)
7b	8-benzyl-7-oxo-4,5,7,8,9,10-hexahydro-10a*H*-thieno[3′,2′:-3,4]pyrido[1.2-*c*]pyrimidine	68	oil	$C_{17}H_{18}N_2OS$ (298.4)	298[c]	1.70–3.51 (m, 7H); 4.48–5.02 (m, 4H); 6.74 (d, 1H, J = 5 Hz); 7.09 (d, 1H, J = 5 Hz); 7.29 (s, 5H)
8	2-methyl-9,10-dimethoxy-4-oxo-1,2,3,4,6,7-hexahydro-11a*H*-pyrimido[6,1-*a*]isoquinoline	27	oil	$C_{15}H_{20}N_2O_3$ (276.3)	276	1.22, 1.29 (each d, 3H, J = 7 Hz); 1.71–3.50 (m, 6H); 3.88 (s, 6H); 4.61–4.72 (m, 2H); 6.69 (br. s, 1H); 6.82 (br. s, 1H)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.25, H ±0.13, N ±0.22.

[b] High-resolution M.S.: calc. 352.1785 (M^+), found 352.1789.

[c] High-resolution M.S.: calc. 298.1138 (M^+), found 298.1135.

unidentified products which are discarded. Subsequent elution with methanol/chloroform (1/99; 120 ml) affords the cyclization product **6**, **7**, or **8**.

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[1] D.J. Hart, *J. Org. Chem.* **46**, 367 (1981).
J.A.M. Hamersma, W.N. Speckamp, *Tetrahedron* **38**, 3255 (1982); and references cited therein.
M.S. Harley, F.D. King, R.T. Martin, *Tetrahedron Lett.* **24**, 91 (1983).
B.E. Maryanoff, D.F. McComsey, B.A. Duhl-Emswiler, *J. Org. Chem.* **48**, 5062 (1983); and references cited therein.

[2] H. Kohn, Z.-K. Liao, *J. Org. Chem.* **47**, 2787 (1982).

[3] S. Kano, Y. Yuasa, T. Yokomatsu, S. Shibuya, *J. Org. Chem.* **48**, 3835 (1983).

[4] S. Kano, Y. Yuasa, T. Yokomatsu, S. Shibuya, *Chem. Lett.* **1983**, 1475.

[5] D. Frehel, J.P. Maffrand, *Heterocycles* **20**, 1731 (1983).

[6] D. Frehel, J.P. Maffrand, *Heterocycles* **22**, 143 (1984).

[7] W.L.F. Armarego, *Fused pyrimidines*, Part I, D.J. Brown, ed., Interscience Publishers, New York, 1967.

[8] J.A. Blanchette, E.V. Brown, *J. Am. Chem. Soc.* **74**, 1066 (1952).

[9] M.L. Mihailovic, M. Tot, *J. Org. Chem.* **22**, 652 (1957).