Lithiated Thiolactams: New Synthesis of Azacycloalka[2,3-*b*]quinolin-4-ones

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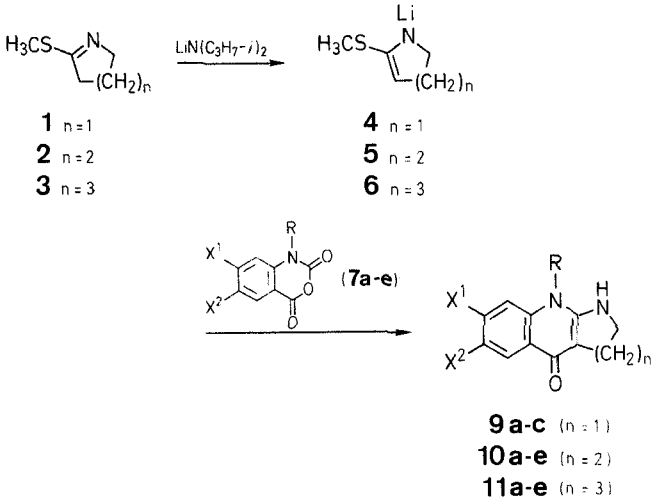
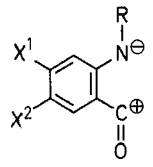
Lithiated enamines, generated from cyclic thioimidates by treatment with lithium diisopropylamide, react with *N*-alkylisatoic anhydrides to afford azacycloalka[2,3-*b*]quinolin-4-ones.

Because of its versatility, the thioamide group plays an important role in synthetic methodology[1,2]. In particular, the thiolactam has been utilized in the synthesis of many natural products[3-8]. Although metallo-ketene-*S*,*N*-acetals derived from cyclic thioimidates may be regarded as interesting metalated enamines, their chemistry has scarcely been studied[9]. We embarked on studies to apply the reaction

employing metalated enamines to heterocyclic synthesis. We describe here a new synthesis azacycloalka[2,3-*b*]quinolin-4-ones by the reaction of lithiated enamines (**4**, **5**, and **6**) with *N*-alkylisatoic anhydrides (**7a–e**) as dipolarophilic synthon (**8**)[10,11].

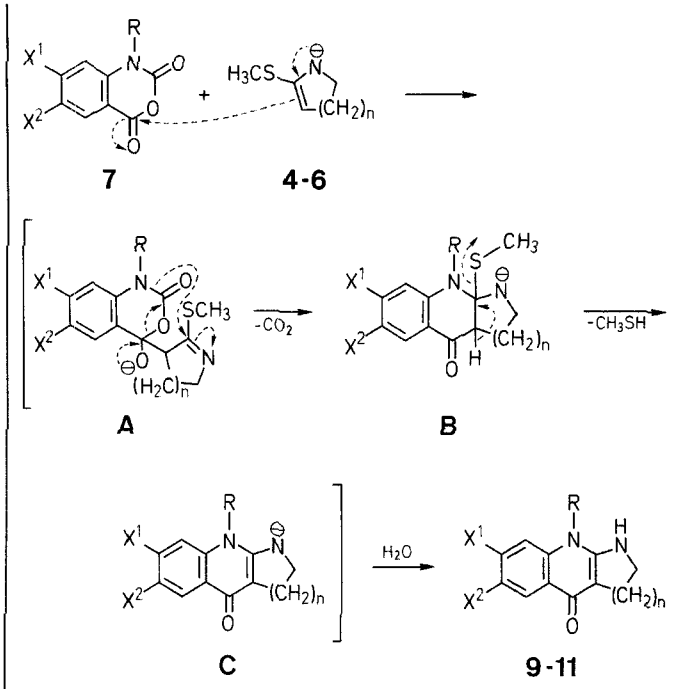


7-10	R	X^1	X^2
a	CH_3	H	H
b	$C_6H_5CH_2$	H	H
c	CH_3	H	CH_3
d	CH_3	Cl	H
e	$C_6H_5CH_2$	Cl	H



Scheme A

Two equivalents of lithiated enamines (**4**, **5**, and **6**), generated from cyclic thioimidates (**1**, **2**, and **3**) by treatment with lithium diisopropylamide (0 °C, 1 h, tetrahydrofuran), react with *N*-alkylisatoic anhydrides (**7a–e**) (– 78 °C, 1 h → room temperature, 4 h–15 h) to afford azacycloalka[2,3-*b*]quinolin-4-ones (**9a–c**, **10a–e**, and **11a–e**), respectively. Functionalized 4-quinolines are of pharmacological inter-



Scheme B

Table. Compounds **9a–c**, **10a–e**, and **11a–e** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[b] δ [ppm]
9a	53 (48)[c]	282–284°	$C_{12}H_{12}N_2O$ (200.2)	3200, 1610, 1595	3.62 (s, 3H, N—CH_3); 5.06 (br. s, 1H, NH)
9b	35	> 300°	$C_{18}H_{16}N_2O$ (276.3)	3160, 1610, 1595	4.51 (br. s, 1H, NH); 5.29 (s, 2H, N—$CH_2C_6H_5$)
9c	41	> 300°	$C_{13}H_{14}N_2O$ (214.3)	3140, 1625, 1595	2.44 (s, 3H, Ar—CH_3); 3.63 (s, 3H, N—CH_3); 5.10 (br. s, 1H, NH)
10a	64 (62)[c]	261–264°	$C_{13}H_{14}N_2O$ (214.3)	3180, 1610, 1595	3.62 (s, 3H, N—CH_3); 4.58 (br. s, 1H, NH)
10b	53	> 300°	$C_{19}H_{18}N_2O$ (290.4)	3180, 1615, 1595	4.27 (br. s, 1H, NH); 5.32 (s, 2H, N—$CH_2C_6H_5$)
10c	42	> 300°	$C_{14}H_{16}N_2O$ (228.3)	3300, 1620, 1585	2.42 (s, 3H, Ar—CH_3); 3.60 (s, 3H, N—CH_3); 4.75 (br. s, 1H, NH)
10d	62	297–299°	$C_{13}H_{13}ClN_2O$ (248.7)	3220, 1610, 1585	3.58 (s, 3H, N—CH_3); 4.54 (br. s, 1H, NH)
10e	14	297–299°	$C_{19}H_{17}ClN_2O$ (324.8)	3220, 1610, 1585	4.31 (br. s, 1H, NH); 5.27 (s, 2H, N—$CH_2C_6H_5$)
11a	25 (28)[c]	221–223°	$C_{14}H_{16}N_2O$ (228.3)	3260, 1610, 1590	3.68 (s, 3H, N—CH_3); 4.32 (br. s, 1H, NH)
11b	31	243–245°	$C_{20}H_{20}N_2O$ (304.4)	3300, 1610, 1595	4.06 (br. s, 1H, NH); 5.36 (s, 3H, N—$CH_2C_6H_5$)
11c	18	264–266°	$C_{15}H_{18}N_2O$ (242.3)	3250, 1620, 1580	2.43 (s, 3H, Ar—CH_3); 3.65 (s, 3H, N—CH_3); 4.38 (br. s, 1H, NH)
11d	24	268–270°	$C_{14}H_{15}ClN_2O$ (262.7)	3210, 1610, 1585	3.65 (s, 3H, N—CH_3); 4.33 (br. s, 1H, NH)
11e	42	254–256°	$C_{20}H_{19}ClN_2O$ (338.8)	3220, 1610, 1580	4.03 (br. s, 1H, NH); 5.30 (s, 3H, N—$CH_2C_6H_5$)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ± 0.46, H ± 0.21, N ± 0.20.
[b] Only selected values are given.
[c] Reactions were carried out on a large scale [**4**, **5**, or **6** (30 mmol)].

est[12–17]. Reaction of **4** with **7d, e** gave intractable mixtures and **9d, e** could not be isolated. The structures assigned to compounds **9, 10**, and **11** were unambiguously confirmed by the I.R.- and ^{1}H-N.M.R. spectral data.

The formation of **9, 10**, and **11** may possibly be explained by a mechanism as shown in Scheme **B**. An attack of the metalated enamine (**4, 5**, or **6**) on the 4-carbonyl group of isatoic anhydrides (**7**) may generate the intermediate **A**. Cyclization of **A** with loss of carbon dioxide may furnish **B**. Subsequent elimination of methyl mercaptan from **B** may produce **C**, which yields **9, 10**, or **11** after work-up.

This method should be applicable to the synthesis of a variety of other azacycloalka[2,3-*b*]quinolin-4-ones by using available cyclic thioimidates.

9-Alkyl-4-oxo-3,4-dihydro-1*H*,4*H*,9*H*-pyrrolo[2,3-*b*]quinolines (9a–c), 10-Alkyl-5-oxo-1,2,3,4-tetrahydro-5*H*,10*H*-benzo[*g*]naphthyridines (10a–e), and 11-Alkyl-6-oxo-2,3,4,5-tetrahydro-1*H*,6*H*,11*H*-azepino[2,3-*b*]quinolines (11a–e); General Procedure:
A 15% solution of *n*-butyllithium in hexane (4 ml, 6 mmol) is added to a cooled tetrahydrofuran solution (12 ml) of diisopropylamine (0.61 g, 6 mmol) at 0 °C with stirring under argon. To this mixture, the cyclic thioimidate **1, 2**, or **3** (6 mmol) is injected. After this mixture is stirred for 1 h at 0 °C, *N*-alkylisatoic anhydride **7a–e** (3 mmol) in tetrahydrofuran (20 ml) is injected into the mixture at −78 °C. After stirring for 1 h at −78 °C, the mixture is gradually warmed to room temperature and stirred for additional hours (4 h for **9a–c**; 15 h for **10a–e** and **11a–e**). The mixture is hydrolyzed by addition of aqueous ammonium chloride solution (10 ml) and extracted with ethyl acetate (3 × 20 ml). The organic layers are combined, dried with magnesium sulfate, and evaporated. The residue is purified by column chromatography on silica gel using chloroform/methanol (9:1) for **9a–c**, (19:1) for **10a–e**, or (100:3) for **11a–e** as eluent. Further purification is achieved by recrystallization from methanol/diisopropyl ether.

Caution! *Diisopropyl ether readily forms peroxides and may explode on shaking.*

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