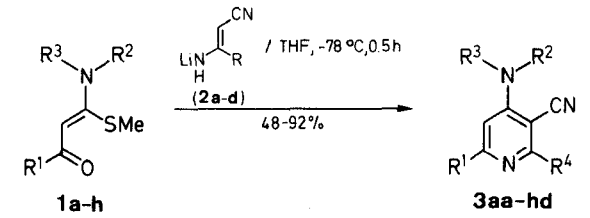
Cyclocondensation of α-Oxoketene *N,S*-Acetals with β-Lithioamino-β-Substituted Acrylonitriles: A Facile Route to 2,6-Substituted 4-Amino-3-cyanopyridines

Janagani Satyanarayana, Hiriyakkanavar Ila*, Hiriyakkanavar Junjappa*
Department of Chemistry, North-Eastern Hill University, Shillong 793003, Meghalaya, India

A novel synthesis of a variety of 2,6-substituted and 3-cyano-4-dialkylamino-2,6-diheteroarylpyridines (4-dialkylamino≡pyrrolidin-1-yl, piperidino, morpholino, diethylamino and *N*-methylanilino; 6-heteroaryl≡phenyl, anisyl, 2-thienyl; 2-heteroaryl≡methyl, phenyl, 2-furyl and 2-thienyl) has been developed by the reaction of α-oxoketene *N,S*-acetals **1** with β-substituted β-lithioaminoacrylonitriles **2**, generated in situ by either self condensation of lithioacetonitrile or by its reaction with substituted acetonitriles.

We have recently reported[1] a facile general route for 2,6-substituted and fused 3-cyano-4-methylthiopyridines through cyclization of α-oxoketene dithioacetals with β-substituted β-lithioaminoacrylonitriles **2** which were generated in situ either by self condensation of lithioacetonitrile or by its reaction with substituted nitriles. The new pyridine synthesis has been exemplified by a variety of substituentes (alkyl/aryl/heteroaryl) which can be introduced in 2,6-positions and has an additional advantage of readily transformable methylthio and nitrile substituents for elaborating to other functional groups. However, our attempts to displace methylthio group in these pyridines by secondary amines like pyrrolidine or morpholine in dimethylformamide were unsuccessful and at elevated reaction temperatures, either no reaction occurred or decomposition of substrates predominated. We therefore considered an alternative route involving the reaction of α-oxoketene *N,S*-acetals **1** with β-lithioaminoacrylonitriles **2** to afford 4-dialkylaminopyridines **3**. These pyridines possess basic/nucleophilic character of special interest.[2-4] We herein report the results of this investigation.

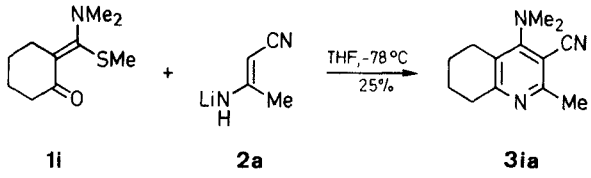
In a typical experiment, **2a** (R^4 = Me) generated in situ treating excess of acetonitrile (3 equiv) with butyllithium (1.5 equiv) was reacted with **1a**, and the product isolated (67%) after work-up was characterized as 3-cyano-2-methyl-4-pyrrolidino-6-phenylpyridine (**3aa**) on the basis of its spectral and analytical data. Other acyclic *N,S*-acetals **1b–f** were similarly reacted with **2a** under identical conditions to afford the corresponding 4-aminopyridines **3ba–fa** in overall high yields (Scheme **1**). Similarly, the reaction of 2-lithioaminocinnamonitrile (**2b**) (generated in situ by treatment of lithioacetonitrile with benzonitrile) with **1** resulted in the formation of 4-amino-2-phenylpyridines **3ab–gb** in 55–92% overall yield. The reaction was equally facile for the synthesis of 4-amino-2,5-dihetarylpyridines **3fc–3fd** through cyclization of **1** with either 2-(2-furyl)- or 2-(thienyl)-β-lithioaminoacrylonitriles (**2c** and **2d**) generated in situ by treatment of lithioacetonitrile with 2-cyanofuran or 2-cyanothiophene, respecitvely. However, extension of this procedure to annulated pyridines was found to have many limitations. Thus the *N,S*-acetal **1i** was obtained in overall low yield and decomposed during purification. The reaction of crude **1i** with **2a** gave tetrahydroquinoline **3ia** in only 25% yield (Scheme **2**).



1a-h **3aa-hd**

Scheme 1

1	R^1	R^2	R^3	2	R^4
a	Ph	$-(CH_2)_4-$		**a**	Me
b	Ph	$-(CH_2)_5-$		**b**	Ph
c	4-$MeOC_6H_4$	$-(CH_2)_5-$		**c**	2-furyl
d	Ph	$-(CH_2)_2O(CH_2)_2-$		**d**	2-thienyl
e	Ph	Me	Ph		
f	2-thienyl	$-(CH_2)_4-$			
g	Ph	Et	Et		
h	2-furyl	$-(CH_2)_4-$			



1i **2a** **3ia**

Scheme 2

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H-NMR spectra on a Varian EM-390 spectrometer and mass spectra on a Jeol JMS-D-300 mass spectrometer.

The starting oxoketene *N,S*-acetals **1a–i** were prepared according to the earlier reported procedure.[5]

2,6-Substituted 3-Cyano-4-dialkyl (or arylalkyl)aminopyridines 3a–i; General Procedure:

To a stirred solution of MeCN (0.82 g, 0.02 mol) in anhydrous THF (25 mL), is added BuLi (10 mmol) under N_2 atmosphere at −78 °C and the mixture is further stirred for 45 min at the same temperature to give reddish suspension of β-lithioaminocrotonitrile (**2a**). For the in situ generation of β-substituted β-lithioaminoacrylonitriles **2b–d**, equimolar quantities of MeCN (0.41 g, 0.01 mol), BuLi (10 mmol) and substituted nitriles i.e. benzonitrile, 2-cyanofuran or 2-cyanothiophene (0.01 mmol) are used. To the suspension of lithioaminoacrylonitriles **2**, the appropriate oxoketene *N,S*-acetals (0.005 mol) in anhydrous THF (25 mL) is added and the mixture is further stirred at this temperature (−78 °C) for 0.5 h. It is warmed up to r.t. and stirring is continued for 48 h. In most cases the reaction is complete after 48 h, while in a few cases (**3aa, 3da, 3fa, 3ab, 3db**) the reaction mixture requires further heating at 60 °C for 2–5 h (monitored by TLC). It is then poured over sat NH_4Cl (150 mL) solution, extracted with Et_2O, (2 × 100 mL) dried and evaporated to give dark brown residues which are purified by column chromatography over silica gel using EtOAc/hexane (1:10) as eluent (Table).

Table. Pyridines **3aa–ia** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS m/z (%)
3aa	67	126	$C_{17}H_{17}N_3$ (263.3)	2220, 1592, 1510, 1480, 1445, 1775, 700	1.80–2.20 (m, 4H, CH_2), 2.62 (s, 3H, CH_3), 3.48 (br s, 4H, NCH_2), 6.19 (s, 1H, H-5), 7.31–7.7 (m, $5H_{arom}$)	263 (M^+, 49), 234 (100)
3ba	91	140–141	$C_{18}H_{19}N_3$ (277.4)	2210, 1590, 1495, 1445, 1245, 1205, 1025, 775, 700	1.66 (br s, 6H, CH_2), 2.60 (s, 3H, CH_3), 3.66 (br s, 4H, NCH_2), 6.35 (s, 1H, H-5), 7.45 (br s, $5H_{arom}$)	277 (M^+, 100), 248 (78), 234 (41)
3ca	92	142–143	$C_{19}H_{21}N_3O$ (307.4)	2200, 1585, 1562, 1507, 1238, 1018, 818	1.65 (br s, 6H, CH_2), 2.63 (s, 3H, CH_3), 3.68 (br s, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 6.42 (s, 1H, H-5), 7.02 (d, 2H, J = 9.0), 7.53 (d, $2H_{arom}$, J = 9)	307 (M^+, 100), 278 (80)
3da	85	168–169	$C_{17}H_{17}N_3O$ (279.3)	2190, 1590, 1578, 1525, 1475, 1240, 1190, 1115, 1005, 885, 685	2.66 (s, 3H, CH_3), 3.52–4.05 (m, 8H, CH_2), 6.50 (s, 1H, H-5), 7.55 (br s, $5H_{arom}$)	279 (M^+, 82), 248 (100)
3ea	89	156–157	$C_{20}H_{17}N_3$ (299.4)	2218, 1590, 1580, 1500, 1400, 705	2.70 (s, 3H, CH_3), 3.54 (s, 3H, NCH_3), 6.23 (s, 1H, H-5), 7.13–7.55 (m, $10H_{arom}$)	299 (M^+, 100), 223 (20)
3fa	55	137–141	$C_{15}H_{15}N_3S$ (269.4)	2235, 1615, 1515, 1478, 1435, 1360, 830, 740	1.90–2.20 (m, 4H, CH_2), 2.65 (s, 3H, CH_3), 3.43–3.74 (m, 4H, NCH_2), 6.35 (s, 1H, H-5), 7.21 (m, $1H_{thienyl}$, H-4'), 7.50 (d, $1H_{thienyl}$, J = 4, H-3'), 7.81 (d, $1H_{thienyl}$, J = 2.5, H-5')	269 (M^+, 41), 240 (56)
3ab	78	173–174	$C_{22}H_{19}N_3$ (325.4)	2220, 1592, 1575, 1510, 1480, 1450, 1348, 700	1.95 (br s, 4H, CH_2), 3.52 (br s, 4H, NCH_2), 6.30 (s, 1H, H-5), 7.33–7.77 (m, $8H_{arom}$), 7.85–8.15 (m, $2H_{arom}$)	325 (M^+, 72), 296 (100)
3db	88	214–215	$C_{22}H_{19}N_3O$ (341.4)	2196, 1585, 1565, 1435, 1197, 1115, 960, 700	3.80 (br s, 8H, CH_2), 6.57 (s, 1H, H-5), 7.35–7.83 (m, $8H_{arom}$), 7.83–8.15 (m, $2H_{arom}$)	341 (M^+, 25), 240 (70)
3eb	92	190–191	$C_{25}H_{19}N_3$ (361.4)	2220, 1590, 1575, 1495, 1400, 1125, 702	3.60 (s, 3H, CH_3), 6.40 (s, 1H, H-5), 7.20–7.60 (m, $13H_{arom}$), 7.92–8.13 (m, $2H_{arom}$)	361 (M^+, 100)
3gb	55	140–141	$C_{22}H_{21}N_3$ (327.4)	2205, 1600, 1595, 1525, 1385, 700	1.25 (t, 6H, J = 7, CH_3CH_2), 3.62 (q, 4H, J = 7, CH_3CH_2), 6.43 (s, 1H, H-5), 7.38–7.75 (m, $8H_{arom}$), 7.85–8.10 (m, $2H_{arom}$)	327 (M^+, 41), 298 (100)
3fc	55	178–179	$C_{18}H_{15}N_3OS$ (321.4)	2200, 1605, 1595, 1500, 1420, 1345, 1160, 745	2.05 (br s, 4H, CH_2), 3.60 (br s, 4H, NCH_2), 6.40 (s, 1H, H-5), 6.61 (m, $1H_{furyl}$), 7.16–7.38 (m, $1H_{thienyl}$), 7.40–7.95 (m, $4H_{thienyl/furyl}$)	321 (M^+, 95), 293 (72), 292 (100)
3hd	45	176–177	$C_{18}H_{15}N_3OS$ (321.4)	2210, 1605, 1590, 1500, 1420, 1350, 740	2.10 (br s, 4H, CH_2), 3.60 (br s, 4H, NCH_2), 6.42 (s, 1H, H-5), 6.65 (m, $1H_{furyl}$), 7.15–7.38 (m, $1H_{thienyl}$), 7.40–7.85 (m, $4H_{thienyl/furyl}$)	321 (M^+, 66), 292 (70)
3fd	48	173–174	$C_{18}H_{15}N_3S_2$ (337.4)	2195, 1588, 1491, 1428, 814, 713	2.01 (br s, 4H, CH_2), 3.60 (br s, 4H, NCH_2), 6.30 (s, 1H, H-5), 7.06–7.30 (m, $2H_{thienyl}$), 7.55 (d, $2H_{thienyl}$, J = 6), 7.81 (d, $1H_{thienyl}$, J = 3), 8.42 (d, $1H_{thienyl}$, J = 3)	337 (M^+, 89), 308 (100)
3ia	25	101–102	$C_{13}H_{17}N_3$ (215.3)	2953, 2933, 2202, 1571, 1500, 1429, 1413, 1391, 1211	1.52–2.02 (m, 4H, CH_2), 2.52 (s, 3H, CH_3), 2.65–3.10 (m, 4H, CH_2), 2.95 [s, 6H, $(CH_3)_2N$]	215 (M^+, 89), 200 (97), 182 (97)

[a] Yield of pure isolated product.
[b] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.22, N ± 0.26.

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