Lithiation of Heterocycles Directed by α-Amino Alkoxides

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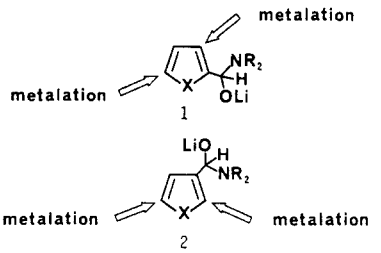
Received June 17, 1986

The addition of heterocyclic aromatic aldehydes to certain lithium dialkylamides gave α-amino alkoxides that were ring-lithiated with butyllithium. Alkylation and hydrolysis provided ring-substituted heterocyclic aromatic aldehydes via a one-pot reaction. The metalation of α-amino alkoxides derived from thiophenecarboxaldehydes, furaldehydes, *N*-methylpyrrolecarboxaldehydes, and indolecarboxaldehydes was examined. The regioselectivity of the lithiation was dependent on the heterocycle, the amine component of the α-amino alkoxide, and the metalation conditions. A novel N-methyl metalation of α-amino alkoxides derived from *N*-methylpyrrole-2-carboxaldehyde and *N*-methylindole-2-carboxaldehyde was achieved when *N,N,N'*-trimethylethylenediamine was used as the amine component for in situ formation of the α-amino alkoxides. These novel directed N-methyl lithiations are attributed to an intramolecular TMEDA-like assisted metalation.

The directed metalation of heterocycles has been receiving considerable attention.[1] Various ortho-directing groups have been utilized to direct lithiation into the 2- or 3-position of thiophenes, furans, pyrroles, and indoles. The regioselectivity of metalation can be dependent on the directing group, the heterocycle, solvent, metalating agent, reaction time, and temperature. Metalations of furans, thiophenes, and 1-methylpyrroles directed by secondary and tertiary carboxamido or oxazolino groups have been studied extensively, and the synthetic value of this methodology has been determined.[2]

We recently reported that α-amino alkoxides could be formed in situ via the addition of aromatic aldehydes to certain lithium dialkylamides. These aryl α-amino alkoxides could be ortho-lithiated, alkylated, and hydrolyzed on workup to provide ortho-substituted aryl aldehydes via a one-pot reaction.[3] We found the directing power of an α-amino alkoxide could be altered by simply varying the amine component, allowing regioselective control during the metalation of a diactivated benzene ring. For example, 4-methoxybenzaldehyde was treated with lithiated *N,N,N'*-trimethylethylenediamine (LTMDA) to form an α-amino alkoxide in situ, which was metalated and alkylated to give 4-methoxy-2-methylbenzaldehyde on aqueous workup in 90% yield. When lithium *N*-methylpiperazide (LNMP) was utilized as the amine component, metalation, methylation, and workup provided 4-methoxy-3-methylbenzaldehyde as the sole product in 73% yield.[3c]

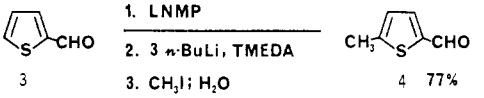
It appeared that the regioselective control inherent in this methodology had considerable potential for the substitution of various aromatic heterocyclic carboxaldehydes. We envisioned that regioselective control might be achieved in heterocyclic systems such as **1** and **2** by varying the amine component of the α-amino alkoxide. By using a strongly directing amine component, i.e., *N,N,N'*-trimethylethylenediamine, lithiation–alkylation should occur adjacent to the α-amino alkoxide group. When a



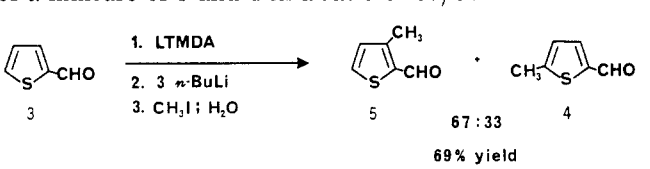
"blocking" amine component is utilized, lithiation–alkylation at a remote site on the heterocyclic ring would be anticipated. We have explored the α-amino alkoxide directed lithiation of various thiophenes, furans, pyrroles, and indoles, and the results of our studies are presented here.

Results and Discussion

Thiophenes. It is well-established that most 2-substituted thiophenes are metalated in the 5-position.[1] However, when the 2-substituent is the strongly ortho-directing oxazoline,[2] a lithiated carboxylic acid,[4] or a secondary carboxamide function,[2] metalation can be directed mainly to the 3-position. Our first reaction was performed by using 2-thiophenecarboxaldehyde (**3**) and lithium *N*-methylpiperazide to form the α-amino alkoxide in situ.



Metalation, alkylation, and workup gave 5-methyl-2-thiophenecarboxaldehyde (**4**) in 77% yield. This was the anticipated result since an α-amino alkoxide group formed from *N*-methylpiperazine is not a strong directing group.[3c] To determine if lithiation could be directed to the 3-position, we performed a metalation reaction using *N,N,N'*-trimethylethylenediamine as the amine component. Although 3-substitution was the major product under all conditions studied, significant amounts of 5-substitution occurred, and the best conditions found gave a 69% yield of a mixture of **5** and **4** in a ratio of 67/33.



To determine if 3,5-disubstituted 2-thiophenecarboxaldehydes could be prepared by this method, we treated 5-methyl-2-thiophenecarboxaldehyde (**4**) with lithiated

(1) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1–360. (b) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (c) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312. (d) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957–986. (e) Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, *7*, 95–106.

(2) (a) Carpenter, A. J.; Chadwick, D. J. *J. Org. Chem.* **1985**, *50*, 4362. (b) Carpenter, A. J.; Chadwick, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 173. (c) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *26*, 5335. (d) Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1343.

(3) (a) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (b) Comins, D. L.; Brown, J. D. *Ibid.* **1983**, *24*, 5465. (c) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

(4) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *26*, 1777.

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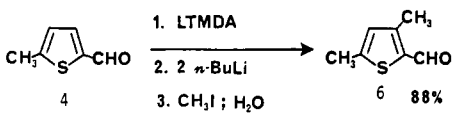
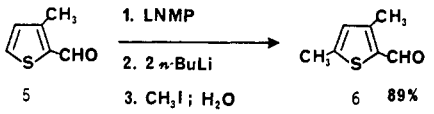
Table I. Alkylation of 3-Thiophenecarboxaldehyde

entry	amine component	metalation conditions[a]	yield,[b] %	product mixture[c]
a	LNMP	3 *n*-BuLi, TMEDA, −23 °C, 3 h	42	mainly starting material
b	LNMP	1.5 *sec*-BuLi, TMEDA, −43 °C, 2 h	75	considerable dimetalation and starting material
c	LNMP	1.2 *sec*-BuLi, TMEDA, −78 °C, 2 h	72	83% 5-methyl-3-thiophenecarboxaldehyde (**8**); 17% 2-methyl-3-thiophenecarboxaldehyde (**9**)
d	LNMP	1.2 *t*-BuLi, −78 °C, 1.5 h	60	40% starting material, 60% 2,5-dialkylation
e	LDA	2 LDA, −20 °C, 5 h	46	mainly starting material and **9**
f	LDA	1.5 *sec*-BuLi, −78 °C, 2 h	43	78% **11**, 22% **9**
g	LTMDA	1.5 *n*-BuLi, −20 °C, 16 h	57	2,5-dialkylation and **9**
h	LTMDA	3 LDA, −20 °C, 16 h	62	80% **9**, 20% starting material
i	LTMDA	1.1 LDA, 0.9 *n*-BuLi, −20 °C, 16 h	78	94% **9**, 6% starting material

[a] All reactions were performed on a 3-mmol scale in THF using excess methyl iodide as the electrophile. [b] Yields are of products mixtures obtained from radial preparative layer chromatography (silica gel, EtOAc–hexanes). [c] Products ratios determined by GC or ^{1}H NMR.

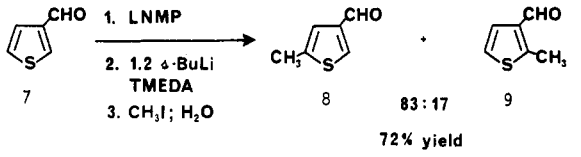
N,N,N'-trimethylethylenediamine, *n*-butyllithium, and methyl iodide. An 88% yield of 3,5-dimethyl-2-





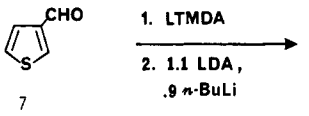
thiophenecarboxaldehyde (**6**) was isolated, demonstrating that effective α-amino alkoxide directed metalation at the 3-position can be obtained if the 5-position is blocked toward lithiation by an alkyl group. A 3,5-disubstituted 2-thiophenecarboxaldehyde can also be obtained starting from a 3-substituted 2-thiophenecarboxaldehyde. Thiophene **5** was substituted at the 5-position to give 3,5-dimethyl-2-thiophenecarboxaldehyde (**6**) in 89% yield.

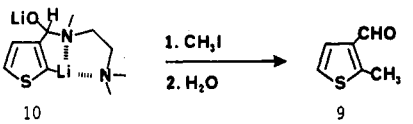
We next turned our attention to the lithiation of α-amino alkoxides derived from 3-thiophenecarboxaldehyde (**7**). Several reactions were performed in an attempt to obtain regioselective metalation at the 2- and 5-positions. The



results are given in Table I. The best conditions found for regioselective 5-substitution utilized *N*-methylpiperazine as the amine component and *sec*-butyllithium/TMEDA at −78 °C (entry C). Alkylation with methyl iodide and workup gave a 72% yield of a mixture of thiophenecarboxaldehydes **8** and **9** in a ratio of 83/17. Although complete regioselectivity was not achieved, this result is significant when compared to the metalation of thiophenes substituted in the 3-position with ortho directing groups such as carboxamides[5] or acetals,[6] which give substitution in the 2-position with high regioselectivity. It is interesting that a similar α-amino alkoxide directed metalation reaction was reported by Gronowitz and co-workers to give 2,3-disubstituted thiophenes. They treated 3-thienyllithium with *N,N*-dimethylformamide, which formed an α-amino alkoxide in situ, lithiated with alkyllithium, and added *N,N*-dimethylacetamide, carbon dioxide, or butylborate to give 2-substituted 3-formylthiophenes on aqueous workup. The yields were low (10–40%), however, and the regioselectivity of the α-amino alkoxide lithiation may have been due to the metalation conditions (refluxing ether).[7]

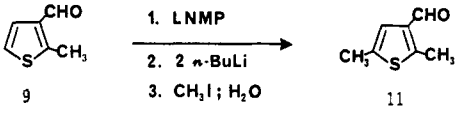
When we attempted to direct metalation to the 2-position by using *N,N,N'*-trimethylethylenediamine as the amine component and excess *n*-butyllithium as the base, lithiation occurred primarily in the 2-position along with 2,5-dimetalation. We were able to overcome the di-



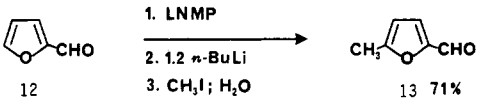


metalation problem by using a mixture of *n*-butyllithium and lithium diisopropylamide for lithiation. This result can be explained by the fact that the acidity of the α-protons of thiophene are very close to that of diisopropylamine. This allows the lithiation to occur under thermodynamic conditions that favor the 2-lithiated thiophene intermediate **10**; one would not expect lithium diisopropylamide to be a sufficiently strong base to form the trianion that is required to produce the 2,5-dialkylated product.

To show that a 2-substituted 3-thiophenecarboxaldehyde could be further alkylated, we metalated thiophene **9** using *N*-methylpiperazine as the amine component and excess *n*-butyllithium as base. After addition of methyl iodide and workup, 2,5-dimethyl-3-thiophenecarboxaldehyde (**11**) was isolated in 54% yield.

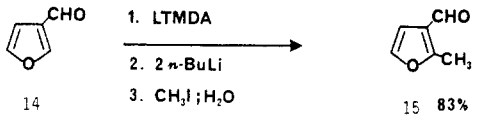


Furans. The α-amino alkoxides derived from 2- and 3-furaldehydes were less responsive than their sulfur counterparts to regioselective control during the metalation step. For example, 2-furaldehyde (**12**) was metalated via an α-amino alkoxide exclusively at the 5-position regardless of which amine component was used. When the α-amino alkoxide was formed using lithium *N*-methylpiperazide and metalated with 1.2 equiv of *n*-butyllithium at −23 °C, methylation and workup provided 5-methyl-2-furaldehyde (**13**) in 71% yield.

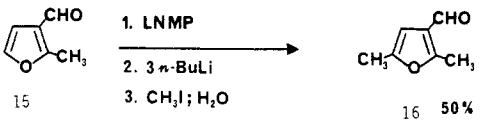


(5) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457.
(6) MacDowell, D. W. H.; Patrick, T. B. *J. Org. Chem.* **1966**, *31*, 3592.
(7) Michael, U.; Gronowitz, S. *Acta Chem. Scand.* **1968**, *22*, 1353.

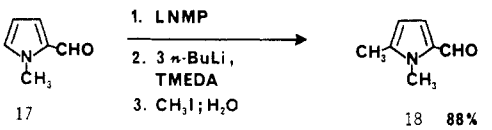
With 3-furaldehyde (14) lithiation occurred at the 2-position with high regioselectivity regardless of which α-amino alkoxide was utilized. The use of *N,N,N'*-trimethylethylenediamine as the amine component gave the cleanest reaction to provide 2-methyl-3-furaldehyde (15) in high yield with regioselectivity of greater than 96%.

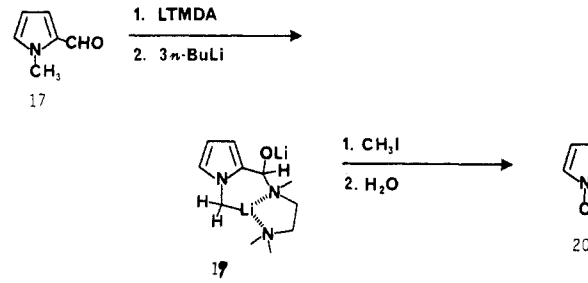


Furaldehyde **15** was substituted at the 5-position by using *N,N,N'*-trimethylethylenediamine as the amine component, *n*-butyllithium as the base, and methyl iodide as the electrophile to give 2,5-dimethyl-3-furaldehyde (**16**) in 50% yield.

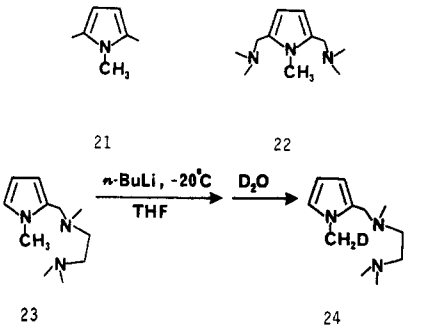


***N*-Methylpyrrole.** There are many reported examples of 1-methylpyrrole being metalated in the α-position.[1a,8] In our study using 1-methyl-2-pyrrolecarboxaldehyde (**17**), α-lithiation was achieved regiospecifically at the 5-position by using lithium *N*-methylpiperazide to form the α-amino alkoxide and treatment with excess *n*-butyllithium/TMEDA in benzene at room temperature. Methylation and workup gave 1,5-dimethyl-2-pyrrolecarboxaldehyde (**18**) as the only isolated product in 88% yield. We attempted to achieve β-lithiation using *N,N,N'*-trimethylethylenediamine as the amine component and excess *n*-butyllithium as the metalation base. Surprisingly, lithiation occurred with high regioselectivity *on the N-methyl group.* Addition of methyl iodide and aqueous workup gave *N*-ethyl-2-pyrrolecarboxaldehyde (**20**) in 74% yield.

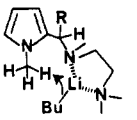




Although N-methyl metalation of azoles has been reported,[9] this is the first example of a directed lithiation on the N-methyl group of an *N*-methylpyrrole. Because of the novelty of this reaction, we looked briefly at the lithiation of three other substituted *N*-methylpyrroles. Attempted lithiation (*n*-BuLi; *sec*-BuLi/TMEDA; *t*-BuLi; etc.) of pyrroles **21** and **22** under various conditions failed, and unchanged starting material was recovered in all cases. The pyrrole **23** did lithiate quantitatively on the N-methyl group under relatively mild conditions to give deuterated compound **24** on treatment with D_2O.

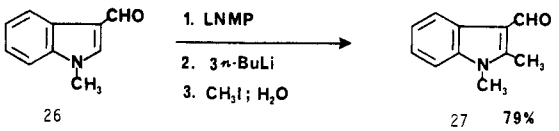


The pyrrole **23** is similar in structure to the α-amino alkoxide leading to **19**. This successful metalation (**19**) and the N-methyl metalation of **23**, and the failure to metalate **21** and **22**, demonstrate the importance of the intramolecular TMEDA-like effect[3c] in directed metalations of this type. Since the acidity of a pyrrole *N*-methyl group appears to be relatively low, the transition state approaching kinetic deprotonation (see **25**) must be highly favorable due to the intramolecular TMEDA-like effect. A related case was observed in the lithiation of α-amino alkoxides derived from *o*-tolualdehyde.[3c] The α-amino alkoxide derived from lithiated *N,N,N'*-trimethylethylenediamine metalates at the *o*-methyl group. However, if piperidine is used as the amine component, ring-lithiation occurs at the other ortho position.[3c]

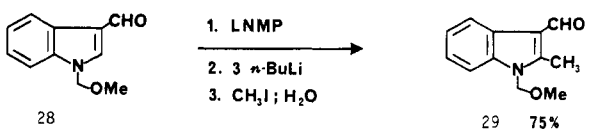


25 R = H, OLi

Indoles. The only reported metalations of 1-substituted indoles are reactions where lithiation occurs in the 2-position.[1a,8,10] We began our studies with 1-methylindole-3-carboxaldehyde (**26**). As expected, we found that α-amino alkoxides derived from **26** could be cleanly lithiated at the 2-position with excess *n*-butyllithium regardless of which lithiated amine was used to form the α-amino alkoxide. When *N*-methylpiperazine was used as the amine component, the 2-methyl derivative **27** could be prepared in 79% yield.



The attempted metalations via α-amino alkoxides of most N-protected (*N*-benzenesulfonyl, *N*-*tert*-butyloxycarbonyl, *N*-dimethylcarbamyl) indole-3-carboxaldehydes were unsuccessful as decomposition occurred. We were successful using the *N*-methoxymethyl derivative **28**, however. The α-amino alkoxide was formed by using *N*-methylpiperazine as the amine component. Lithiation with *n*-butyllithium and methylation gave the 2-methylindole derivative **29** in 75% yield.



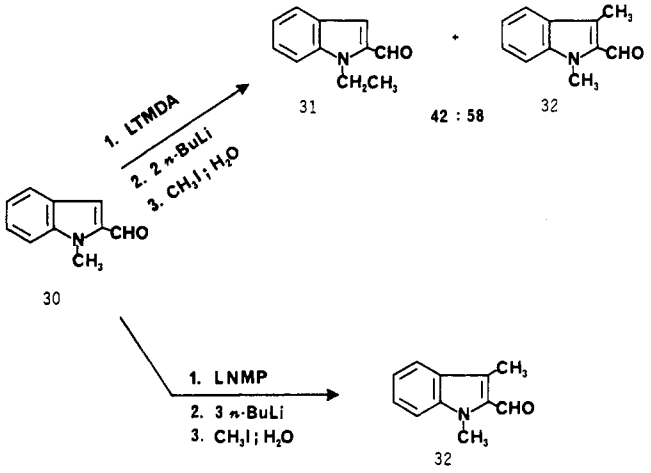
(8) Jones, R. A. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press Ltd: Oxford, 1984; Vol. 4, p 238.
(9) Katritzky, A. R.; Jayaram, C.; Vassilatos, S. N. *Tetrahedron* **1983**, *39*, 2023 and references therein.
(10) Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935.

Table II. Alkylation of 1-Methylindole-2-carboxaldehyde (30)

entry	amine component	metalation conditions[a]	solvent	% SM(30)[b]	% 32[b]
a	LNMP	3 *n*-BuLi, 25 °C, 13 h	THF	36	64
b	LNMP	1.4 *t*-BuLi, −20 °C, 18 h	THF	mainly starting material	
c	LNMP	3 *n*-BuLi, 25 °C, 15 h	benzene	mainly starting material	
d	LNMP	3 *n*-BuLi, reflux, 8 h	benzene	excessive decomposition	
e	LNMP	3 *n*-BuLi, TMEDA, 25 °C, 8 h, reflux, 3 h	ether	15	85
f	LNMP	3 *n*-BuLi, −20 °C, 10 h	DME	40	60
g	LNMP	3 *n*-BuLi, −20 °C, 24 h	DME	40	60
h	LNMP	2 *sec*-BuLi, −23 °C, 5 h	DME	83	17
i	LNMP	3 *n*-BuLi, 25 °C, 40 h	cyclohexane	40	60
j	LNMP	2 *sec*-BuLi, 25 °C, 22 h	cyclohexane	64	34

[a] All reactions were performed on a 2-mmol scale. Methyl iodide was used as the electrophile. [b] Product to starting material ratios were determined by ^{1}H NMR.

We next investigated the metalation of α-amino alkoxides prepared from 1-methylindole-2-carboxaldehyde (**30**). The lithiation–methylation of the α-amino alkoxide prepared from lithiated *N,N,N'*-trimethylethylenediamine gave a mixture of 1-ethylindole-2-carboxaldehyde (**31**) and



1,3-dimethylindole-2-carboxaldehyde (**32**) in a ratio of 42/58. This is the first example of a directed N-methyl metalation of a 1-methylindole derivative. It is also the first example of a directed metalation at the 3-position of an indole. Unfortunately, we were unable to find conditions to improve the ratio of products in favor of N-methyl substitution. The use of *N*-methylpiperazine as the amine component allowed regiospecific metalation to occur in the 3-position; however, as can be seen in Table II, we could not drive the reaction to completion. Refluxing ether/TMEDA and portionwise addition of *n*-butyllithium gave the best results with a starting material to product ratio of 15/85 (entry e). This allowed us to prepare 1,3-dimethylindole-2-carboxaldehyde (**32**) in a regiospecific manner with an isolated yield of 72%.

Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) and ether were dried by distillation from sodium/benzophenone ketyl prior to use. Benzene, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), *N,N,N'*-trimethylethylenediamine, *N*-methylpiperazine, diisopropylamine, hexanes, cyclohexane, ethylene glycol dimethyl ether (DME), and dimethylformamide (DMF) were distilled from calcium hydride and stored over 3-Å molecular sieves under N_2. Heterocyclic aromatic aldehydes from commerical sources were distilled prior to use. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian EM-360 or JEOL FX-90-Q spectrometers and IR spectra were recorded on a Perkin-Elmer 710B spectrometer. Gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5880A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with OV-17 or OV-101. Radial preparative layer chromatography was carried out by using a Chromatotron (Harrison Assoc., Palo Alto, CA). Combustion analyses were performed by M.H.W. Laboratories, Phoenix, AZ. The 2,4-dinitrophenylhydrazones were prepared by using a recently published modified method.[11]

5-Methyl-2-thiophenecarboxaldehyde (4). To a solution of 0.40 mL (3.6 mmol) of *N*-methylpiperazine in 10 mL of THF at −78 °C was added a hexane solution of *n*-BuLi (3.31 mmol). After 15 min, 0.26 mL (3 mmol) of 2-thiophenecarboxaldehyde was added and the mixture was stirred at −78 °C for 15 min. TMEDA (1.36 mL, 9 mmol) and *n*-BuLi (9 mmol) in hexane were added and the mixture was allowed to stir at −23 °C for 3 h. Methyl iodide (1.1 mL, 18 mmol) was added dropwise at −78 °C and the mixture was allowed to come to room temperature (30 min). The mixture was then poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 20:80) to give 290 mg (77%) of **4** as a light yellow oil: ^{1}H NMR (CCl_4) δ 9.85 (s, 1 H), 7.65 (d, J = 4 Hz, 1 H), 6.93 (d, J = 4 Hz, 1 H), 2.59 (s, 3 H). (This product was identical with an authentic sample purchased commercially.)

Preparation of 3,5-Dimethyl-2-thiophenecarboxaldehyde (6) from Thiophenecarboxaldehyde 5. To a solution of 0.40 mL (3.6 mmol) of *N*-methylpiperazine in 10 mL of THF at −78 °C was added 3.3 mmol of *n*-BuLi in hexane. After 15 min, 379 mg (0.32 mL, 3 mmol) of 3-methyl-2-thiophenecarboxaldehyde (**5**) was added and stirring was continued for an additional 15 min. A hexane solution of *n*-BuLi (6 mmol) was added and the mixture was allowed to stir at −23 °C for 3 h. Methyl iodide (1.1 mL, 18 mmol) was added at −78 °C and the mixture was allowed to come to room temperature (30 min). The mixture was poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 30:70) to give 412 mg (89%) of **6** as a light yellow oil: ^{1}H NMR (CCl_4) δ 10.03 (s, 1 H), 6.83 (s, 1 H), 2.5[illegible] (s, 6 H); *p*-nitrophenylhydrazone, mp 221–223 °C (EtOAc) (lit.[12] mp 221–223 °C).

Preparation of 3,5-Dimethyl-2-thiophenecarboxaldehyde (6) from 4. By following the above procedure, except using *N,N,N'*-trimethylethylenediamine and 5-methyl-2-thiophenecarboxaldehyde (**4**), 3,5-dimethyl-2-thiophenecarboxaldehyde (**6**) was obtained in 88% yield.

5-Methyl-3-thiophenecarboxaldehyde (8). To a solution of 0.40 mL (3.6 mmol) of *N*-methylpiperazine in 10 mL of THF at −78 °C was added 3.3 mmol of *n*-BuLi in hexane. After 15 min, 0.26 mL (3 mmol) of 3-thiophenecarboxaldehyde was added and the mixture was allowed to stir for an additional 15 min. TMEDA

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(0.91 mL, 6 mmol) and a hexane solution of *sec*-BuLi (3.6 mmol) were added, and the mixture was stirred at −78 °C for 2 h. Methyl iodide (0.73 mL, 12 mmol) was added dropwise and the mixture was allowed to come to room temperature (30 min). The mixture was poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. By GC analysis the crude product was composed of 14% SM, 14% 2-methyl-3-thiophenecarboxaldehyde (**9**), and 72% of **8**. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 20:80) to give 270 mg (72%) of **8** as a light yellow oil: ^1H NMR (CCl_4) δ 9.88 (s, 1 H), 8.00 (s, 1 H), 7.20 (s, 1 H), 2.53 (s, 3 H); semicarbazone, mp 206–207.5 °C (EtOAc) (lit.[13] mp 206–207.5 °C).

2-Methyl-3-thiophenecarboxaldehyde (9). To a solution of 0.46 mL (3.6 mmol) of *N,N,N'*-trimethylethylenediamine in 10 mL of THF at −78 °C was added 3.3 mmol of *n*-BuLi in hexane. After 5 min, 333 mg (0.26 mL, 3 mmol) of 3-thiophenecarboxaldehyde was added, and the mixture was allowed to stir for an additional 15 min. Diisopropylamine (0.47 mL, 3.3 mmol) and a hexane solution of *n*-BuLi (6 mmol) were added and the flask was sealed and put in a freezer (−20 °C) for 6 h. Methyl iodide (0.73 mL, 12 mmol) was added at −78 °C and the mixture was allowed to come to room temperature (30 min). The mixture was poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 20:80) to give 272 mg (72%) of **9** as a light yellow oil: ^1H NMR (CCl_4) δ 10.10 (s, 1 H), 7.37 (d, J = 5.5 Hz, 1 H), 7.07 (d, J = 5.5 Hz, 1 H), 2.76 (s, 3 H); acid mp 113–114 °C (lit.[14] mp 112–114 °C) [The acid was prepared by Ag_2O oxidation and recrystallization from water].

2,5-Dimethyl-3-thiophenecarboxaldehyde (11). To a solution of 0.22 mL (2 mmol) of *N*-methylpiperazine in 8 mL of THF at −78 °C was added 1.8 mmol of *n*-BuLi in hexane. After 15 min, 201 mg (1.6 mmol) of 2-methyl-3-thiophenecarboxaldehyde (**9**) was added, and the mixture was allowed to stir for an additional 15 min. A hexane solution of *n*-BuLi (3 mmol) was added and the mixture was allowed to stir at −23 °C for 3 h. Methyl iodide (0.73 mL, 12 mmol) was added at −78 °C, and the mixture was allowed to warm to room temperature (30 min). The mixture was poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 20:80) to give 129 mg (54%) of **11** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 9.90 (s, 1 H), 6.97 (s, 1 H), 2.69 (s, 3 H), 2.30 (s, 3 H); phenylhydrazone mp 95–96 °C (EtOH–H_2O) (lit.[15] mp 95–96 °C).

5-Methyl-2-furaldehyde (13). To a solution of 0.40 mL (3.66 mmol) of *N*-methylpiperazine in 10 mL of THF at −78 °C was added 3.3 mmol of *n*-BuLi in hexane. After 15 min, 288 mg (0.25 mL, 3 mmol) of 2-furaldehyde has added and the mixture was allowed to stir for an additional 15 min. A hexane solution of *n*-BuLi (3 mmol) was added and the mixture was stirred at −23 °C for 5 h. Methyl iodide (0.73 mL, 4 mmol)) was added at −78 °C and the mixture was allowed to come to room temperature (30 min). The mixture was then poured into vigorously stirred cold brine (20 mL) and extracted with ether. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 20:80) to give 233 mg (71%) of **13** as a clear oil: ^1H NMR (CCl_4) δ 9.57 (s, 1 H), 7.20 (d, J = 4 Hz, 1 H), 6.30 (d, J = 4 Hz, 1 H), 2.43 (s, 3 H). (This product was identical with an authentic sample purchased commerically.)

2-Methyl-3-furaldehyde (15). To a solution of 0.46 mL (3.6 mmol) of *N,N,N'*-trimethylethylenediamine in 10 mL of THF at −78 °C was added 3.3 mmol of *n*-BuLi in hexane. After 15 min, 291 mg (0.26 mL, 3 mmol) of 3-furaldehyde was added and the mixture was allowed to stir for an additional 15 min. A hexane solution of *n*-BuLi (6 mmol) was added and the mixture was stirred for an additional 2 h at −78 °C. Keeping the temperature at −78 °C, methyl iodide (1.1 mL, 18 mmol) was added dropwise and the solution was allowed to warm to room temperature (30 min). The mixture was poured into vigorously stirred brine (20 mL) and extracted with ether. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, CH_2Cl_2–hexanes, 10:90) to give 280 mg (83%) of **15** as a clear oil: ^1H NMR ($CDCl_3$) δ 9.93 (s, 1 H), 7.30 (d, J = 2 Hz, 1 H), 6.65 (d, J = 2 Hz, 1 H), 2.60 (s, 3 H); DNP mp 228–229 °C (EtOAc) (lit.[16] mp 229 °C).

2,5-Dimethyl-3-furaldehyde (16). To a solution of 0.46 mL (3.6 mmol) of *N,N,N'*-trimethylethylenediamine in 10 mL of THF at −78 °C was added 3.3 mmol of *n*-BuLi in hexane. After 15 min, 320 mg (3 mmol) of 2-methyl-3-furaldehyde was added and the mixture was allowed to stir for 15 min. A hexane solution of *n*-BuLi (9 mmol) was added and the solution was stirred at −23 °C for 3 h. Methyl iodide (1.1 mL, 18 mmol) was addeed dropwise at −78 °C and the mixture was allowed to come to room temperature (30 min). The mixture was poured into vigorously stirred brine (20 mL) and extracted with ether. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 10:90) to give 180 mg (50%) of **16** as a clear oil: ^1H NMR (CCl_4) δ 10.00 (s, 1 H), 7.03 (s, 1 H), 2.56 (s, 3 H), 2.20 (s, 3 H); DNP mp 228–230 °C (lit.[17] mp 228–230 °C).

1,5-Dimethyl-2-pyrrolecarboxaldehyde (18). To a solution of 0.40 mL (3.6 mmol) of *N*-methylpiperazine in 10 mL of benzene at 0 °C was added 3.3 mmol of *n*-BuLi in hexane. A white precipitate formed. After 15 min, 306 mg (0.32 mL, 3 mmol) of 1-methyl-2-pyrrolecarboxaldehyde was added and the mixture was allowed to stir for an additional 15 min. TMEDA (1.36 mL, 9 mmol) and a hexane solution of *n*-BuLi (9 mmol) were added, and the mixture was allowed to stir at room temperature for 12 h. The solution was cooled to 0 °C and THF (10 mL) was added. The mixture was further cooled to −42 °C and methyl iodide (1.1 mL, 18 mmol) was added dropwise. After 5 min at −42 °C, the mixture was allowed to come to room temperature (30 min). The mixture was poured into vigorously stirred cold water and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 20:80) to give 324 mg (88%) of **18** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 9.33 (s, 1 H), 6.77 (d, J = 4 Hz, 1 H), 5.92 (d, J = 4 Hz, 1 H), 3.77 (s, 3 H), 2.18 (s, 3 H); IR (neat) 1655, 1490, 1360, 1150, 1035, 785 cm^{-1} (lit.[18]); DNP mp 227–228 °C.

1-Ethyl-2-pyrrolecarboxaldehyde (20). To a solution of 0.46 mL (3.6 mmol) of *N,N,N'*-trimethylethylenediamine in 10 mL of THF at −78 °C was added 3.3 mmol of *n*-BuLi in hexane. After 15 min, 306 mg (0.32 mL, 3 mmol) of 1-methyl-2-pyrrolecarboxaldehyde was added and the mixture was allowed to stir for 15 min. A hexane solution of *n*-BuLi (9 mmol) was added and the flask was sealed and placed in a freezer (−20 °C) for 14 h. Methyl iodide (1.1 mL, 18 mmol) was added dropwise at −78 °C, and the mixture was allowed to warm to room temperature (30 min). The mixture was poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 20:80) to give 275 mg (74%) of **20** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 9.50 (s, 1 H), 6.91 (m, 2 H), 6.20 (m, 1 H), 4.30 (q, J = 7 Hz, 2 H), 1.33 (t, J = 7 Hz, 3 H); phenylhydrazone mp 75 °C (lit.[19] mp 75 °C).

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1,2-Dimethylindole-3-carboxaldehyde (27). To a solution of 0.27 mL (2.4 mmol) of *N*-methylpiperazine in 8 mL of THF at −78 °C was added 2.2 mmol of *n*-BuLi in hexane. After 15 min, 320 mg (2 mmol) of 1-methylindole-3-carboxaldehyde was added and the mixture was allowed to stir for an additional 15 min. A hexane solution of *n*-BuLi (6 mmol) was added and the mixture was stirred at −23 °C for 3 h. Methyl iodide (0.73 mL, 12 mmol) was added at −78 °C and the mixture was allowed to warm to room temperature (30 min). The mixture was poured into vigorously stirred cold water (20 mL) and extracted with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 30:70) to give 273 mg (79%) of **27** as a white solid: mp 129–131 °C (lit.[20] mp 131–132 °C) (benzene–hexanes); ^1H NMR ($CDCl_3$) δ 10.09 (s, 1 H), 8.16–8.35 (m, 1 H), 7.16–7.39 (m, 3 H), 3.59 (s, 3 H), 2.57 (s, 3 H).

Preparation of 1-(Methoxymethyl)indole-3-carboxaldehyde (28). Sodium hydride (60% dispersion in oil, 1.26 g, 31.5 mmol) was washed twice with dry hexanes and suspended in THF (20 mL). The mixture was cooled to −23 °C and indole-3-carboxaldehyde (4.35 g, 30 mmol) in 30 mL of THF was added dropwise. After warming to room temperature and stirring for 30 min, the solution was cooled to −23 °C and chloromethyl methyl ether (2.50 mL, 33 mmol) was added, and the mixture was allowed to come to room temperature (45 min). The mixture was poured into vigorously stirred cold 5% aqueous sodium bicarbonate (30 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated to give a solid. The crude product was purified by Kugelrohr distillation (175–180 °C (1 mm)) followed by recrystallization using a hexanes–EtOAc mixture to give 4.685 g (83%) of **28** as a white crystalline solid: mp 77.5–78.5 °C; ^1H NMR ($CDCl_3$) δ 9.93 (s, 1 H), 8.16–8.31 (m, 1 H), 7.69 (s, 1 H); 7.13–7.55 (m, 3 H), 5.35 (s, 2 H), 3.19 (s, 3 H); IR (KBr) 1610, 1445, 1375, 1175, 1090, 735 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.75; H, 6.00; N, 7.47.

1-(Methoxymethyl)-2-methylindole-3-carboxaldehyde (29). To a solution of 0.43 mL (3.98 mmol) of *N*-methylpiperazine in 10 mL of THF at −78 °C was added 3.6 mmol of *n*-BuLi in hexane. After 15 min, 629 mg (3.3 mmol) of 1-(methoxymethyl)indole-3-carboxaldehyde (**28**) was added and the mixture was stirred for an additional 15 min. A hexane solution of *n*-BuLi (9 mmol) was added and the mixture was stirred at −23 °C for 3 h. Methyl iodide (1.2 mL, 19.8 mmol) was added at −78 °C and the mixture was allowed to come to room temperature (30 min). The mixture was poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 30:70) to give 479 mg (75%) of **29** as a white solid: mp 94–95 °C (hexanes, EtOAc) (lit.[21] mp 87–90 °C); ^1H NMR ($CDCl_3$) δ 9.98 (s, 1 H), 8.21 (m, 1 H), 7.17–7.50 (m, 3 H), 5.77 (s, 1 H), 3.15 (s, 3 H), 2.46 (s, 3 H).

Preparation of 1-Methylindole-2-carboxaldehyde (30). A hexane solution of *n*-BuLi (3 mmol) was added to 396 mg (0.38 mL, 3 mmol) of 1-methylindole in 10 mL of dry ether and the mixture was heated at reflux for 8 h. The mixture was cooled to −42 °C and dimethylformamide (0.35 mL, 4.55 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h before being poured into stirred cold water (20 mL). After 10 min, the mixture was extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 10:90) to give 389 mg (82%) of **30** as a white solid: mp 84–85 °C (hexanes) (lit.[22] mp 84–85 °C); ^1H NMR (CCl_4) δ 9.93 (s, 1 H), 6.80–7.90 (m, 5 H), 4.07 (s, 3 H).

1,3-Dimethylindole-2-carboxaldehyde (32). To a solution of 0.27 mL (2.4 mmol) of *N*-methylpiperazine in 15 mL of dry ether at 0 °C was added 2.2 mmol of *n*-BuLi in hexane. After 10 min, 310 mg of 1-methylindole-2-carboxaldehyde was added and the mixture was allowed to stir for an additional 15 min. TMEDA (0.45 mL, 3 mmol) and a hexane solution of *n*-BuLi (2 mmol) were added and the mixture was stirred at room temperature for 4 h before an additional 2 mmol of *n*-BuLi was added. After 4 h of stirring at room temperature, 2 mmol of *n*-BuLi in hexane was added and the mixture was heated at reflux for 3 h. The solution was then cooled to −78 °C and THF (10 mL) was added. Methyl iodide (0.73 mL, 12 mmol) was added dropwise over 5 min and the mixture was allowed to warm to room temperature (30 min). The solution was poured into vigorously stirred cold water (20 mL) and extracted with ether. The organic extracts were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated. The crude product was purified by radial preparative layer chromatography (silica gel, EtOAc–hexanes, 10:90) to give 291 mg (86%) of a product as a light yellow oil. By NMR it was determined the title compound composed 85% of the product, while starting material accounted for 15%. Compound **32** was isolated in 72% yield by further purification with radial preparative layer chromatography (silica gel, CH_2Cl_2–hexanes, 10:90) followed by recrystallization (EtOH, H_2O): mp 36–37 °C (lit.[23] mp 36 °C); ^1H NMR ($CDCl_3$) δ 10.11 (s, 1 H), 7.02–7.76 (m, 4 H), 4.00 (s, 3 H), 2.61 (s, 3 H).

Registry No. **3**, 98-03-3; **4**, 13679-70-4; **5**, 5834-16-2; **6**, 85895-83-6; **7**, 498-62-4; **8**, 29421-72-5; **9**, 84815-20-3; **11**, 26421-44-3; **12**, 98-01-1; **13**, 620-02-0; **14**, 498-60-2; **15**, 5612-67-9; **16**, 54583-69-6; **17**, 1192-58-1; **18**, 1193-59-5; **20**, 2167-14-8; **26**, 19012-03-4; **27**, 38292-40-9; **28**, 73540-77-9; **29**, 84543-18-0; **30**, 27421-51-8; **31**, 40913-43-7; **32**, 1971-44-4; LNMP, 105563-31-3; NMP, 109-01-3; LTMDA, 99532-66-8; TMDA, 142-25-6; $ClCH_2OCH_3$, 107-30-2; 1-methylindole, 603-76-9; indole-3-carboxaldehyde, 487-89-8.

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