

# Reactions of lithiated aromatic heterocycles with carbon monoxide

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**ABSTRACT:** The reaction of lithium derivatives of aromatic heterocycles with carbon monoxide was studied under several reaction conditions: 2-furyllithium afforded only one product, the tetrahydro-2-furaldehyde (25% yield). On the other hand, 2-thienyllithium and 5-methyl-2-furyllithium gave two and five products, respectively. Although in relatively low yields, formation of highly functionalized compounds takes place in a fast process under mild conditions. For 1,4-dihydroxy-1,4-bis(5-methyl-2-furanyl)butane-2,3-dione, reaction conditions were achieved to obtain this difficult to prepare derivative in 50% yield. To the best of our knowledge, this is the first report on the reaction of lithiated aromatic heterocycles with CO: evidence is given on the involvement of proton transfers in the reactions of 2-furyllithium and 2-thienyllithium, while the reaction of 5-methyl-2-furyllithium seems to proceed through an electron transfer as the first step. Copyright © 2003 John Wiley & Sons, Ltd.

**KEYWORDS:** mechanism; carbonylation; organolithium; heterocycles; radicals; electron transfer

## INTRODUCTION

The chemistry of five-membered heterocyclic rings is a field of active research.<sup>1</sup> Some furan derivatives have achieved considerable technical importance, since it has been found that the furan ring, in both its native and reduced forms, occurs in a variety of commercially important<sup>2</sup> pharmaceuticals and flavor and fragrance compounds; they can also serve as pivotal intermediates in synthetic strategy by virtue of their specific chemistry and latent functionality.<sup>3</sup> Thiophene has found widespread use in the synthesis of biologically active species, which contain this nucleus either as the central ring or as part of a central fused ring system.<sup>1,4</sup>

Renewed interest in natural product synthesis and for in synthesis of heterocyclic compounds requires reliable methods for the preparation of these starting materials. The usual procedures have the drawback of causing some resinification and degradation of the heterocyclic rings, and some substituted furans and thiophenes have been obtained only by indirect means.<sup>5,6</sup> This justifies the

continued, considerable effort in the development of novel approaches to this class of compounds: we have recently demonstrated the utility of organolithium<sup>7</sup> and organostannane<sup>8</sup> reagents for the preparation of allyl-furans and -thiophenes.

The reaction of organolithium compounds with carbon monoxide has found wide application in organic synthesis,<sup>9,10</sup> and the reaction is interesting also from mechanistic viewpoints. The synthetic usefulness of the carbonylation of organolithium compounds<sup>11</sup> has been demonstrated. In addition, we have recently characterized important intermediates in the reaction between lithium dialkylamides and substituted formamides, affording evidence for the structures of the lithium carbamoyl intermediates and the mechanisms of their further reactions.<sup>12</sup>

It was then of interest to examine the feasibility of the reaction of lithiated derivatives of heteroaromatic compounds with CO. The reaction was examined under several conditions and evidence for the possible mechanisms of carbonylation of 2-furyllithium, 5-methyl-2-furyllithium and 2-thienyllithium was sought. To our knowledge, this is the first report about the mechanism of reactions involving carbanions derived from aromatic heterocycles.

## RESULTS AND DISCUSSION

The lithium derivatives of furans were prepared by direct

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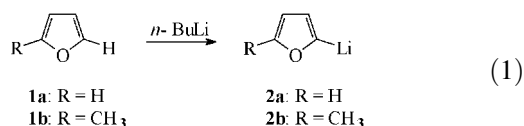
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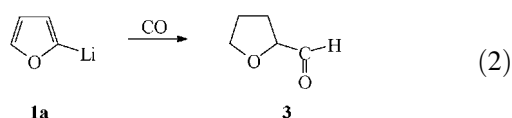
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metalation of furan (**1a**) and of 2-methylfuran (**1b**) with *n*-butyllithium (see Experimental section) [Eqn. (1)].



### Reaction of 2-furyllithium (**2a**) with CO

The carbonylation of 2-furyllithium, carried out in THF at  $-78^\circ\text{C}$ , afforded only one product, the tetrahydro-2-furaldehyde (**3**) [Eqn. (2)] in low yield (20%). The structure of **3** was confirmed by independent synthesis (see Experimental section).



Usually, the furan nucleus is very reactive and the reaction conditions must be carefully controlled in order to avoid polymerization and ring-opening reactions. The temperature of the reaction was the first variable studied but a not significant effect on the product yield was found in the range  $-78$  to  $40^\circ\text{C}$ . This result suggests that the activation energy for this reaction would be not very high. On the other hand, on increasing the temperature, more decomposition of the reagent and formation of polymeric products were observed. Then, the lithium reagent concentration was varied between 0.1 and 0.3 M and no observable effect was detected.

The presence of **3** indicates that in the reaction mixture there exists a source of hydrogen; therefore, it was crucial to analyze the solvent effect; some results are shown in Table 1. In hexane and diethyl ether no CO absorption

**Table 1.** Reaction of 2-furyllithium<sup>a</sup> (**2a**) with CO: solvent effects

Solvent	<i>T</i> ( $^\circ\text{C}$ )	<i>V</i> <sub>CO</sub> (ml)	Yield (%)	
			<b>1a</b>	<b>3</b>
Hexane	$-78$	–	100	–
	0	–	100	–
Hexane–THF (1:1)	$-78$	2.0	94	6
	0	2.2	92	5
Hexane–THF (1:10)	$-78$	3.0	89	9
	0	3.5	90	6
Diethyl ether	$-78$	–	100	–
	0	–	100	–
THF	$-78$	6.0	78	20
	0	9.0	80	20
THF–HMPT (10:1)	$-78$	6.5	75	23
	0	9.3	78	22
THF–HMPT (1:1)	$-78$	7.2	75	25
	0	10.0	75	25

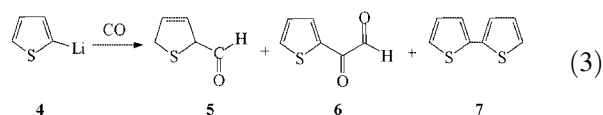
<sup>a</sup> [**2a**] =  $2 \times 10^{-3}$  mol; *t* = 40 min.

was observed; a higher yield of **3** in pure solvents was obtained when the reaction was carried out in THF; addition of HMPT produced a slight increase in the yield of **3**. The fact that **3** is not formed when the reaction was carried out in hexane or diethyl ether suggests that a proton donor such as THF is needed for the reaction to occur. In fact, some amount of THF in hexane was sufficient to obtain small yields of **3**. This could be attributed to a direct THF–lithium interaction, which favors the proton transfer; this type of interaction has been observed in other reactions of organolithium compounds in THF.<sup>13</sup>

Lack of formation of any other product in the reaction suggests that the reaction of **2a** with CO, under all conditions employed, could involve only one mechanistic pathway. (The mechanism is discussed below).

### Reaction of 2-thienyllithium (**4**) with CO

Compound **4** was prepared by metal–halogen exchange between 2-iodothiophene and *n*-butyllithium. The carbonylation of **4**, carried out in THF at  $-78^\circ\text{C}$ , afforded two main products, 2,5-dihydro-2-thiophencarboxaldehyde (**5**) and 2-oxo-2-(2-thienyl)acetaldehyde (**6**), together with small amounts of bithiophene (**7**) [Eqn. (3)].



The structure of **5** was confirmed by independent synthesis (see Experimental section). Variations in the temperature had no significant effects on product distribution.

Table 2 shows the results of the solvent effect: for the reaction carried out in hexane or diethyl ether, **6** was the only product obtained. Upon addition of THF, **5** was also formed, suggesting that proton transfer from THF occurs. On the other hand, the percentages of **5** and **6** were maximum in pure THF.

**Table 2.** Reaction of 2-thienyllithium (**4**) with CO at  $0^\circ\text{C}$ : solvent effects<sup>a</sup>

Solvent	<i>V</i> <sub>CO</sub> (ml)	Yield (%)		
		<b>5</b>	<b>6</b>	<b>7</b>
Hexane	6	–	12	–
Hexane–THF (1:1)	7	–	15	–
Hexane–THF (1:10)	10	5	20	2
Diethyl ether	10	–	25	2
THF	24	17	35	3
THF–HMPT (10:1)	25	20	35	–

<sup>a</sup> [**4**] =  $2 \times 10^{-3}$  mol; *t*<sub>abs</sub> = 70 min.

**Table 3.** Reaction of 5-methyl-2-furyllithium<sup>a</sup> (**2b**) with CO in THF: effect of temperature

<i>T</i> (°C)	<i>V</i> <sub>CO</sub> (ml)	Yield (%)				
		<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>
−78 <sup>b</sup>	12	15	35	5	5	3
0 <sup>c</sup>	16	12	50	5	2	2
25 <sup>c</sup>	12	10	35	5	–	–
40 <sup>d</sup>	10	10	15	–	–	–

<sup>a</sup> [**2b**] = 2 × 10<sup>−3</sup> mol.<sup>b</sup> *t*<sub>abs</sub> = 50 min, **1b**, 35%.<sup>c</sup> *t*<sub>abs</sub> = 40 min, **1b**, 28%.<sup>d</sup> *t*<sub>abs</sub> = 40 min, **1b**, 45%.

### Reaction of 5-methyl-2-furyllithium (**2b**) with CO

In THF at −78 °C, two main products were formed, 5-methyltetrahydro-2-furaldehyde (**8**) and 1,4-dihydroxy-1,4-bis(5-methyl-2-furanyl)butane-2,3-dione (**9**), together with small amounts of (5-methyl-tetrahydro-2-furanyl)-(5-methyl-2-furanyl)methanol (**10**), 2-hydroxy-2-(5-methyl-2-furanyl)acetaldehyde (**11**) and bis(5-methyl-2-furanyl)methanol (**12**) [Eqn. (4)].

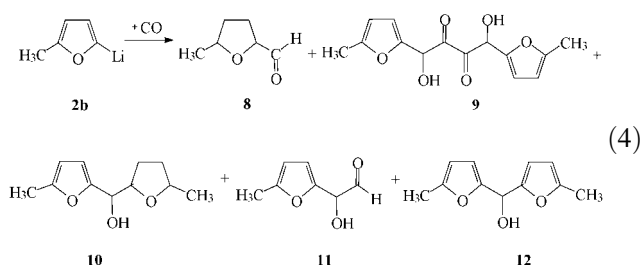


Table 3 shows the effect of temperature on the reaction rate and product distribution of the carbonylation carried out in THF. It can be observed that the reaction proceeds slightly faster at 0 °C and the CO absorption was higher than at −78 °C. The yield of **9** increased at 0 °C, whereas **8** and **10–12** were obtained in poor yields. Attempts to

**Table 4.** Reaction of 5-methyl-2-furyllithium (**2b**) with CO at 0 °C: solvent effects<sup>a</sup>

Solvent	<i>V</i> <sub>CO</sub> (ml)	Yield (%)				
		<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>
Hexane	6	–	20	–	2	–
Hexane–THF (1:1)	9	4	25	–	2	–
Diethyl ether	10	–	35	–	2	2
THF	16	12	50	5	2	2

<sup>a</sup> [**2b**] = 2 × 10<sup>−3</sup> mol; *t* = 40 min.

increase the yield of **9** by increasing the temperature were unsuccessful. At higher temperatures the CO absorption was lower, the organolithium reagent was not totally recovered and polymeric products were obtained.

The structure of 5-methyl-tetrahydro-2-furaldehyde (**8**) was confirmed by independent reduction of 5-methyl-2-furaldehyde with H<sub>2</sub>/Pd (C). Table 4 shows the results of the carbonylation of **2b** at 0 °C in several pure and binary solvents. In all cases the main product was **9**; the reduction products **8** and **10** were not observed in pure hexane or diethyl ether. The maximum CO absorption and the highest yields were obtained in pure THF, indicating that proton transfer from THF occurs.

### Effect of radical traps

Earlier work by our group had shown that the carbonylation of aryllithium compounds occurs through the intermediacy of paramagnetic species.<sup>11a,14</sup> In order to gather information concerning radical involvement in the reaction of **2b** with CO, the reaction was carried out in the presence of a suitable radical trap (Table 5). Quinones and hydroquinones can produce stable radicals by one-electron uptake or donation<sup>15</sup> and they were previously used to test the involvement of radicals in the carbonylation of lithium amides;<sup>16</sup> therefore, they were considered suitable to test the presence of radicals in the carbonylation of **2b**.

**Table 5.** Reaction of 5-methyl-2-furyllithium (**2b**)<sup>a</sup> with CO in THF in the presence of radical inhibitors

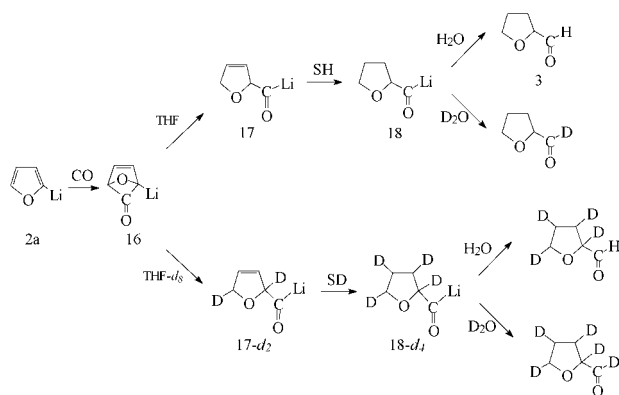
Inhibitor	<i>T</i> (°C)	[Trap]:[ <b>2b</b> ]	<i>t</i> <sub>T</sub> (min)	<i>V</i> <sub>CO</sub> (ml)	Yield (%)				
					<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>
None	−78	–	50	12	15	35	5	5	3
	0	–	40	16	12	50	5	2	2
<i>p</i> -Hydroquinone <sup>b</sup>	−78	1:10	25	4.0	12	15	4	–	–
	0	1:10	25	4.0	10	10	3	–	–
Quinhydrone <sup>b</sup>	−78	1:10	25	3.9	13	15	3	–	–
	0	1:10	25	4.0	10	10	3	–	–
Iodine <sup>b</sup>	−78	1:10	25	4.0	12	15	4	–	–
	0	1:10	25	4.0	10	10	3	–	–

<sup>a</sup> [**2b**] = 1.3 × 10<sup>−3</sup> mol.<sup>b</sup> [**1b**] = 73%.

The reaction was examined in THF at  $-78$  and  $0^\circ\text{C}$  in the presence of radical scavengers, namely *p*-hydroquinone (**13**), quinhydrone (**14**), and iodine (**15**). As shown in Table 5, a considerable decrease in the CO absorption in the presence of **13–15** occurs, and 73% of the reagent was recovered as **1b**. It is important to note the drastic lowering of the yield of **9** and the complete absence of **11** and **12**, whereas **8** and **10** were obtained in similar yields which were found when the reaction was carried out in the absence of inhibitors. On the other hand, in the presence of iodine in a ratio of 1:1 (not shown), total inhibition of carbonylation was observed. These observations indicate that the reaction of **2b** with CO partially involves a radical pathway and that **13–15** must have trapped the radical precursors of **9**, **11** and **12**. The fact that the yields of **8** and **10** were similar under both conditions suggests that the pathway leading to these compounds does not involve radical intermediates.

### Proposed mechanism for the reaction of 2-furyllithium (**2a**) with CO

Interestingly, no reaction products with the intact furan aromatic ring were found. This, together with the absence of radical reaction intermediates, suggests that a mechanism different from that previously reported for the carbonylation of aryllithiums could be involved. Furan is an excellent diene and the [4 + 2] cycloaddition to dienophiles was one of the earliest described examples of the Diels–Alder reaction;<sup>1,17</sup> e.g. furans undergo cycloaddition with simple dienophiles such as ethylene, singlet oxygen and acrylate.<sup>18</sup> Therefore, addition of CO to **2a** giving the intermediate **16** is proposed as the first step in Scheme 1. The subsequent proton transfer from the solvent gives the intermediate **17**; formation of 2,5-dihydrofuran derivatives has been observed in reactions of diverse electrophilic reagents with furans.<sup>19</sup> Another proton transfer should give the intermediate **18**, which on



Scheme 1

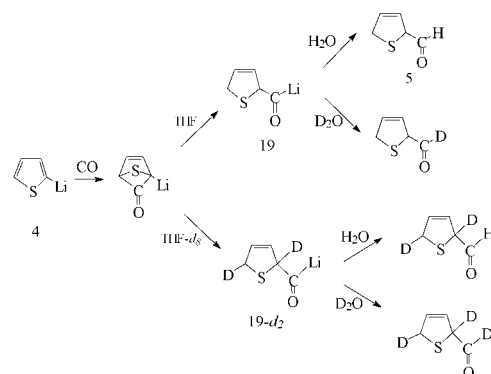
hydrolysis would produce tetrahydro-2-furaldehyde (**3**). The fact that **3** is not obtained when the reaction is carried out in hexane or diethyl ether suggests that proton transfer from THF would occur.

To test the hypothesis that THF should be the hydrogen source, the reaction between **2a** and CO was carried out in THF-*d*<sub>8</sub>. The determination of the deuterium content in **3** revealed approximately 80% deuterium incorporation (see the Experimental section). This result is consistent with the proposed mechanism.

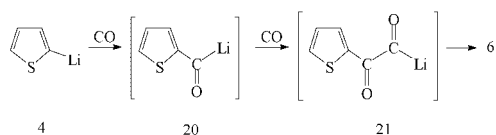
### Proposed mechanism for the reaction of 2-thienyllithium (**4**) with CO

The absence of effects in the presence of radical traps indicates that the reaction does not occur by an electron transfer mechanism. The reaction should rather lead to the formation of **5** by a pathway similar to that suggested for the formation of **3** (Scheme 2), i.e. addition of CO to the dienic system would give the reduced product; in this case, probably owing to the lower electronegativity of sulfur, only partial reduction of the aromatic ring occurs, giving a thienyl intermediate, **19**, similar to **17**. Also in this case, the reaction was carried out in THF-*d*<sub>8</sub>, and almost complete deuteration was observed (see Experimental section).

On the other hand, the higher aromaticity of thiophene vs furan<sup>4,19</sup> would allow an alternative route for carbonylation, similar to that of aryllithiums, affording the formation of product **6** with the intact thiophene ring [see Eqn. (3)]. As outlined in Scheme 3, CO insertion in the C–Li bond would give first the acyllithium intermediate **20**, which by reaction with another molecule of CO forms the intermediate **21**, precursor of the doubly carbonylated product. Similar double carbonylation has been observed in the reaction between lithium amides and CO giving dialkylglyoxylamides and tetraalkyltartroramides in excellent yields.<sup>11b</sup>



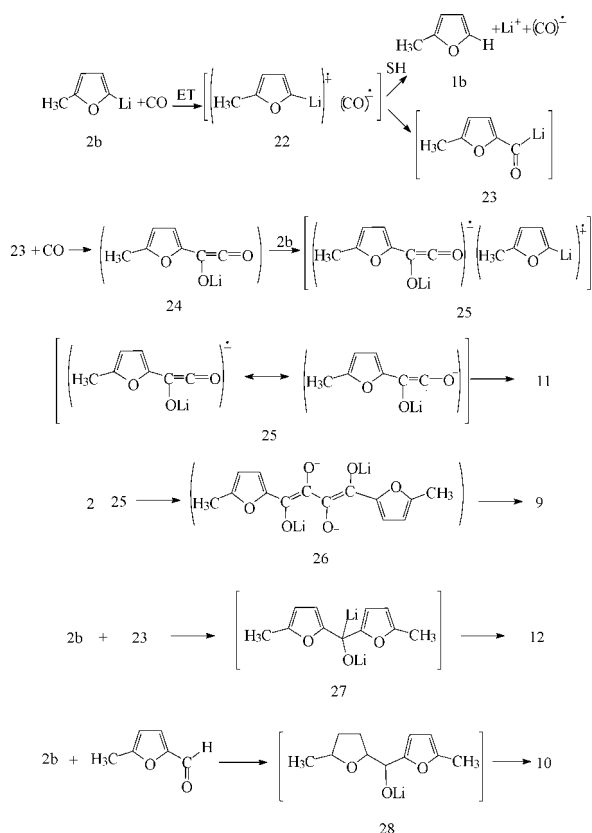
Scheme 2



Scheme 3

### Proposed mechanism for the reaction of 5-methyl-2-furyllithium (**2b**) with CO

The results obtained in the carbonylation of **2b** indicate a complex reaction scheme through, at least, two different routes: radical and polar pathways. The observed decrease in the CO absorption when the reaction was carried out in the presence of radical inhibitors suggests the partial involvement of electron transfer in the first step. Organolithium compounds have been shown to be good one-electron donors to carbonyl compounds<sup>20</sup> and CO is a known electron-deficient compound and an effective one-electron oxidant toward a variety of aromatic radical ions.<sup>21</sup> A plausible pathway involving radical ions is outlined in Scheme 4. As shown, an electron transfer from 5-methyl-2-furyllithium (**2b**) to CO generates the radical cation–radical anion pair **22**. The radical pair **22** can then react within the cage affording the acyllithium intermediate **23**. A similar



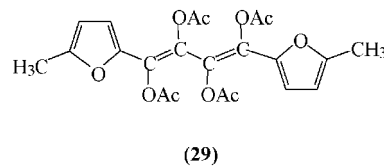
Scheme 4

electron transfer mechanism was previously proved to occur in the reaction of phenyllithium with CO to give an acyllithium intermediate.<sup>14</sup>

The different reactivity pattern exhibited by **2b** compared with **2a** should be due to the methyl group in the  $\alpha$ -position that prevents the 2,5-addition of CO, favors the electron transfer to CO and stabilizes the radical cation **22**. Radical cations of aromatic five-membered heterocycles could be prepared previously by choosing a suitable system<sup>22</sup> and, recently, the radical cations of furans, thiophenes and pyrroles and their oligomers were easily detected by EPR when the adjacent positions to the heteroatom were occupied by alkyl substituents.<sup>23</sup>

The intermediate **23** can take up another molecule of CO to give **24**, which can act as an electron acceptor from another molecule of **2b** forming a new radical cation–radical anion pair, **25**. Our previous *ab initio* calculations on carbamoyllithiums<sup>24</sup> and experimental evidence with arylacyl- and carbamoyllithiums<sup>14</sup> indicate that these intermediates exhibit a strong oxycarbene character. The radical anion in **25** can partially escape the cage being the precursor of **11**. A resonance structure of **25** is written as a radical anion; coupling of two molecules would form **26**, precursor of **9**.

In order to gather more evidence about the mechanism of the reaction, the carbonylation of **2b** was carried out in THF at 0°C and acetic anhydride was added prior to work-up. Only one main compound, **29**, was obtained, which was characterized as the tetraacetyl derivative 1,2-bis-2-(5-methylfuryl)-1,2,3,4-tetraacetylbutene (**29**). The isolation and characterization of **29** confirmed the structure of the intermediate **26** and shed new light on the mechanism of the reaction of **2b** with CO.



On the other hand, the acyllithium intermediate **23** can react with **2b** yielding intermediate **27**, which gives **12** on hydrolysis.

Compound **8** could be formed by the same pathway that was suggested for the formation of **3** from **2a** with no radical involvement, as indicated by its regular formation in the presence of radical traps. When the reaction was carried out in THF-*d*<sub>8</sub>, 76% deuterium incorporation was observed (see Experimental section), confirming that the proton transfer occurs from THF. Further reaction with **2b** gives **28**, precursor of **10** (Scheme 4).

Very little has been published about the mechanism of the reaction of furyl- and thienyllithium and to the best of our knowledge this is the first report on the reaction of CO with heteroaryllithium compounds.

## EXPERIMENTAL

All reactions involving organolithium reagents were carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.<sup>25</sup> GLC analyses were carried out on a Hewlett-Packard Model 5890 Series II Plus gas chromatograph using an HP-5 column with temperature programming from 60 to 250 °C. NMR spectra were recorded on a Bruker 200 spectrometer. Mass spectra were recorded on a BG Trio-2 spectrometer. The percentage deuterium incorporation in products, when applicable, was calculated on the basis of mass spectrometric (MS) data.

### Solvents and reagents

**Materials.** Distilled THF, diethyl ether and hexane were refluxed over sodium benzophenone ketyl until a dark blue solution was obtained and then distilled immediately before use under dry oxygen-free nitrogen. *n*-Butyllithium was prepared as described previously.<sup>26</sup> The concentration of BuLi was determined by the double titration method described previously.<sup>12</sup> All glassware, syringes and needles were dried in a vacuum oven and cooled in a desiccator. Furan and 2-methylfuran were left over sodium strings for 4–5 h, then refluxed and distilled over sodium and stored in sealed ampoules under nitrogen, which were opened immediately prior to use.

**Lithium furans.** Cooled (0 °C) *n*-BuLi (10 ml, 1 M in hexane) was syringed into a non-air stopper-capped tube under a nitrogen atmosphere, and the corresponding furan (15 mmol) was added; it was kept at –18 °C. 2-Furyllithium precipitated after 72 h and 5-methyl-2-furyllithium precipitated after 15 days.

**2-Thienyllithium.** Cooled (0 °C) *n*-BuLi (10 ml, 1 M in hexane) was syringed into a non-air stopper-capped tube under a nitrogen atmosphere and 2-iodothiophene (10 mmol) was added; the lithium reagent precipitated instantly.

The organolithium compounds were characterized by <sup>13</sup>C NMR spectroscopy; the lithiation causes a clear shift (5–10 ppm) of the signal of the lithiated carbon and of C $\alpha$  relative to the starting material.

**2a:** <sup>13</sup>C NMR (Cl<sub>3</sub>CD),  $\delta$  155.2 (C-1), 126.7 (C-2), 111.5 (C-3), 145.4 (C-4).

**2b:** <sup>13</sup>C NMR (Cl<sub>3</sub>CD),  $\delta$  157.5 (C-1), 125.9 (C-2), 110.2 (C-3), 154.3 (C-4), 13.8 (C-5).

### Reaction of lithiated derivatives of aromatic heterocycles with CO

**General procedure.** A vial containing a PTFE-coated stirring bar was heated in a vacuum oven at 130–150 °C

for at least 30 min and then cooled in a dried nitrogen atmosphere. The vial was capped with a non-air stopper, it was alternately evacuated and filled with dry nitrogen several times, then put into an ice-bath with vigorous magnetic stirring. A lithium reagent solution (0.5 M) in THF was added by cannula and the stirred solution was exposed to carbon monoxide at ca 1013 mbar. Carbon monoxide was generated from 98% formic acid and concentrated sulphuric acid at 100–110 °C. The gas was routinely passed through a column of potassium hydroxide before entering the system. The total amount of gas was measured by means of a burette attached to the CO generator provided with a mercury levelling bulb. Once the reaction was completed, 10% HCl in THF was added and the dried (MgSO<sub>4</sub>) organic phase was quantitatively analyzed by GC and GC–MS. 2,5-Dihydro-2-thiophenecarboxaldehyde (**5**), 2-oxo-2-(2-thienyl)acetaldehyde (**6**), 5-methyltetrahydro-2-furaldehyde (**8**) and 1,4-dihydroxyl-1,4-bis(5-methyl-2-furanyl)butane-2,3-dione (**9**), obtained by carbonylation of respective reagents, were isolated by neutral aluminum oxide chromatography using hexane–ethyl acetate mixtures as eluents.

**In the presence of radical inhibitors.** The reactions were carried out in a flask containing weighed amounts of the inhibitor. The desired volume of the lithium reactant solution was added by syringe and the CO absorption was carried out similarly to the general procedure. The rate of reaction was measured by monitoring the rate of CO absorption. Once the reaction was complete, 10% HCl was added. The dried (MgSO<sub>4</sub>) organic layer was analyzed by GC.

**Tetrahydro-2-furaldehyde (3).** This compound was independently synthesized by hydrogenation of 2-furaldehyde (10 mmol in 20 ml of CH<sub>2</sub>Cl<sub>2</sub>) with H<sub>2</sub> (2 atm) in the presence of 10% Pd(C). The reaction mixture was stirred for 5 h at room temperature. The catalyst was separated by filtration and the solvent removed by distillation at reduced pressure. MS: *m/z* (relative intensity, %), 100 (10.5), 99 (8.2), 71 (100), 43 (88.2). <sup>1</sup>H NMR (Cl<sub>3</sub>CD):  $\delta$  9.10 (s, 1H), 3.65 (m, 2H), 3.18 (m, 1H), 2.55 (m, 2H), 2.0 (m, 2H). <sup>13</sup>C NMR (Cl<sub>3</sub>CD):  $\delta$  198.6, 82.2, 67.2, 26.8, 24.9.

When the reaction of **2a** with CO was carried out in THF-*d*<sub>8</sub>, tetrahydro-2-furaldehyde-*d*<sub>5</sub> (**3-d**<sub>5</sub>) was observed. MS: *m/z* (relative intensity, %), 105 (8.4), 103 (5.3), 100 (2.1), 75 (100), 71 (22.2), 45 (65.0), 43 (17.5).

**2,5-Dihydro-2-thiophenecarboxaldehyde (5).** This compound was independently synthesized by hydrogenation of 2-thiophenecarboxaldehyde (10 mmol in 20 ml of CH<sub>2</sub>Cl<sub>2</sub>) with H<sub>2</sub> (2 atm) in the presence of 10% Pd(C). The reaction mixture was stirred for 2 h at room temperature. The catalyst was separated by filtration and the solvent removed by distillation at reduced pressure. Compound **5** was isolated by neutral aluminum

oxide chromatography from the reaction mixture. MS:  $m/z$  (relative intensity, %), 114 (8.61); 113 (2.0), 85 (45.5), 84 (10.6), 71 (32.2), 57 (45.5), 43 (100).  $^1\text{H}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  9.20 (s, 1H), 5.80 (m, 1H), 5.34 (m, 1H), 4.62 (d, 1H,  $J = 3.5$  Hz), 3.50 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  200.0, 130.2, 124.1, 66.5, 30.5.

When the reaction of **4** with CO was carried out in THF- $d_8$ , 2,5-dihydro-2-thiophenecarboxaldehyde- $d_3$  (**5- $d_3$** ) was observed. MS:  $m/z$  (relative intensity, %), 117 (6.6), 115 (1.5), 114 (2.0), 113 (0.1), 87 (37.2), 85 (0.5), 72 (20.2), 71 (2.3), 58 (37.1), 57 (9.0), 44 (100), 43 (81.0).

**2-Oxo-2-(2-thienyl)acetaldehyde (6)**. This compound (oil) was characterized by analogy with dialkylglyoxylamides,<sup>11b</sup> and was isolated from the reaction mixture by neutral aluminum oxide chromatography. MS:  $m/z$  (relative intensity, %), 140 (31.4), 139 (1.4), 111 (7.2), 97 (100).  $^1\text{H}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  9.60 (s, 1H), 7.90 (dd, 1H,  $J = 4.0, 1.6$  Hz), 7.60 (dd, 1H,  $J = 5.1, 1.6$  Hz), 6.87 (dd, 1H,  $J = 5.1, 4.0$  Hz).  $^{13}\text{C}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  190.6, 181.0, 145.5, 134.4, 132.7, 128.2.

**5-Methyltetrahydro-2-furaldehyde (8)**. This compound was independently synthesized by hydrogenation of 5-methyl-2-furaldehyde (10 mmol in 20 ml of  $\text{CH}_2\text{Cl}_2$ ) with  $\text{H}_2$  (2 atm) in the presence of 10% Pd(C). The reaction mixture was stirred for 5 h at room temperature. The catalyst was separated by filtration and the solvent removed by distillation at reduced pressure. MS:  $m/z$  (relative intensity, %), 114 (6.0), 113 (1.3), 99 (1.5), 85 (10.2), 71 (20.1), 57 (46.5), 43 (100).  $^1\text{H}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  9.08 (s, 1H), 3.73 (m, 1H), 3.22 (m, 1H), 2.55 (m, 2H), 2.2 (m, 2H), 1.37 (d, 3H,  $J = 5.2$  Hz).  $^{13}\text{C}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  195.6, 80.5, 73.8, 32.6, 25.1, 21.6.

When the reaction of **2b** with CO was carried out in THF- $d_8$ , 5-methyltetrahydro-2-furaldehyde- $d_5$  (**8- $d_5$** ) was observed. MS:  $m/z$  (relative intensity, %), 119 (4.5), 117 (0.8), 114 (1.2), 104 (1.8), 99 (0.5), 89 (7.8), 85 (2.2), 74 (15.6), 71 (5.0), 59 (30.0), 57 (11.5), 44 (100), 43 (76.4).

**1,4-Dihydroxy-1,4-bis(5-methyl-2-furanyl)butane-2,3-dione (9)**. Compound **9** (oil) was isolated by neutral aluminum oxide chromatography from the reaction mixture. MS:  $m/z$  (relative intensity, %): 278 (2.0), 235 (2.2), 217 (2.4), 183 (5.0), 109 (16.3), 91 (88.5), 71 (60.6), 55 (95.0), 43 (100).  $^1\text{H}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  6.40 (d, 1H,  $J = 3.8$  Hz), 5.3 (s, 1H), 5.25 (dd, 1H,  $J = 3.8, 1.1$  Hz), 4.05 (s, 1H), 2.2 (d, 3H,  $J = 1.1$  Hz).  $^{13}\text{C}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  197.0, 156.2, 151.1, 107.2, 85.6, 73.2, 14.0.

**1,2-Bis-2-(5-methylfuryl)-1,2,3,4-tetraacetylbutene (29)**. The reaction of **1b** with CO was carried similarly to the general procedure. Once the reaction was complete, acetic anhydride was added. The dried ( $\text{MgSO}_4$ ) organic layer was analyzed by GC and the reaction mixture was separated by neutral aluminum oxide chromatography.

The main fraction corresponded to **29**; white solid recrystallized from ethanol, m.p. 117 °C. MS:  $m/z$  (relative intensity, %), 446 (10.0), 328 (2.0), 223 (5.2), 210 (2.3), 71 (34.5), 55 (76.0), 43 (100).  $^1\text{H}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  6.25 (d, 1H,  $J = 3.5$  Hz), 5.90 (dd, 1H,  $J = 3.5, 0.9$  Hz), 2.15 (d, 3H,  $J = 0.9$  Hz).  $^{13}\text{C}$  NMR ( $\text{Cl}_3\text{CD}$ ):  $\delta$  170.0, 165.2, 154.5, 148.7, 143.2, 136.0, 117.6, 98.5, 20.1, 13.6.

## CONCLUSIONS

This paper reports experimental details about the carbonylation of lithium derivatives of aromatic heterocycles. The reaction of 2-furyllithium with CO in THF afforded only one product, 2-tetrahydrofuraldehyde, which was formed by CO absorption and subsequent proton transfer from the solvent. 5-Methyl-2-furyllithium was more reactive and five products were formed by reaction with CO. Evidence is given that some of them derive from radical intermediates. The different reactivity patterns of the two lithium reagents show that the presence of a methyl group in the  $\alpha$ -position of the furan ring results in a good one-electron donor reacting by an electron transfer mechanism. In contrast, the reaction of 2-thienyllithium led to the formation of 2-dihydrothiophenecarboxaldehyde and a double-carbonylated product, with no evidence of radical intermediates. This work sheds some light on the mechanism of an interesting set of reactions, reported for the first time.

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