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Synthesis of Trisubstituted Furans from 2-Bromo-5-methylfuran *via* Halogen Migrations and Their Selective Preventions

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Summary. New trisubstituted furans exhibiting two different substitution patterns were synthesized *via* lithiation of 2-bromo-5-methylfuran. Choice of appropriate reaction parameters enabled selective halogen dance reactions, affording 2-substituted 3-bromo-5-methylfurans upon quenching with various electrophiles. Moreover, from the same starting material also complete prevention of halogen migration could be achieved, thus providing selective access to 3-substituted 2-bromo-5-methylfurans.

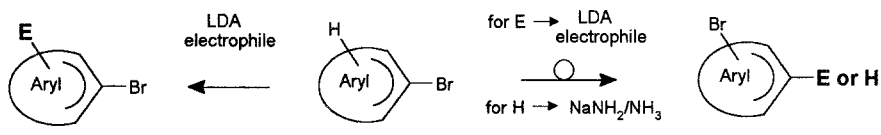
Keywords. 2-Bromo-5-methylfuran; Trisubstituted furans; Halogen dance; Lithiumdiisopropylamide; *LIDAKOR*.

Synthese dreifachsubstituierter Furane aus 2-Brom-5-methylfuran *via* Halogenwanderung und deren selektiver Verhinderung

Zusammenfassung. Durch Lithiierung von 2-Brom-5-methylfuran konnten Furane mit zwei verschiedenen Substitutionsmustern synthetisiert werden. Es wurden Reaktionsbedingungen für eine kontrollierte Halogenwanderungsreaktion entwickelt, durch die nach Quenchen mit verschiedenen Elektrophilen 2-substituierte 3-Brom-5-methylfurane erhalten wurden. An demselben Edukt konnte auch vollständige Hintanhaltung der Umlagerung erzielt werden, wodurch Zugang zu 3-substituierten 2-Brom-5-methylfuranen geschaffen wurde.

Introduction

It is known that certain aryl bromides or iodides rearrange their substitution pattern upon treatment with alkali amide bases, thus producing isomers, usually referred to in literature as halogen migration or halogen dance (HD) reactions (Scheme 1, General Pathway B).



General Pathway A: ***prevention of HD*** General Pathway B: ***halogen dance***

Scheme 1

First observations were made by chance at 2-bromothiophenes, resulting mainly in mixtures of a large number of compounds [1]. Nevertheless, mechanistic investigations were performed [2, 3, 4] and first synthetically useful applications employing the classical potassium amide conditions were developed [5, 6]. An important extension of the scope of this reaction type was published by *Kano* [7]: he for the first time enabled subsequent substitution using *LDA* as base and quenching the generated lithium intermediate with electrophiles. A comprehensive review of amide induced halogen migrations can be found in Ref. [8] and the references cited therein.

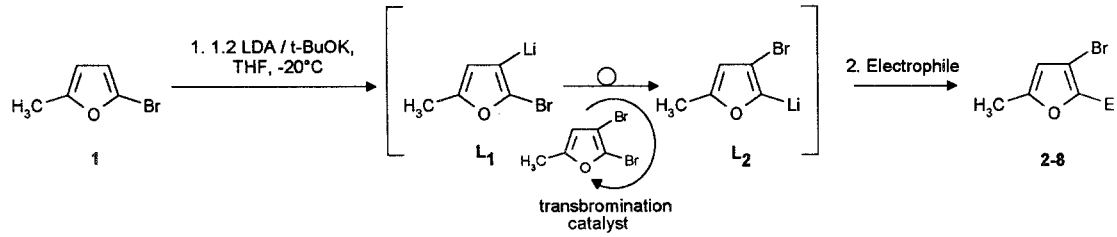
Our own work in this field started with migrations at dibromothiophenes [9, 10] and 2-bromo-5-methylthiophene [11]. The extension of this work towards furans led for the first time to successful halogen dance and prevention of migration at 2,3- and 2,5-dibromofuran [12] at a preparative scale with a wide synthetic scope (Scheme 1, General Pathways A and B) to yield a series of new trisubstituted furans. Our recent results obtained in related areas, in particular with hetero-biaryls, in combination with detailed mechanistic considerations and discussions of selective migration control and prevention of this reaction type are also presented in Ref. [8]. In continuation of our HD-research on furans, we report on the application of the halogen migration methodology to 2-bromo-5-methylfuran as well as the retaining of the substitution pattern at this substrate.

Results and Discussion

Halogen migration

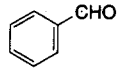
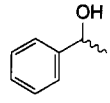
The first experiments to induce halogen dance at 2-bromo-5-methylfuran (**1**) were carried out in analogy to the corresponding thiophene derivative, the migration of which has previously been investigated [11]. A remarkable difference was observed in the metalation behavior between these apparently similar systems: no lithiation at all was observed at the furan derivative **1** employing lithiumdiisopropylamide as a metalating base in *THF*, even on raising the reaction temperature up to $-20\,^{\circ}C$. This unexpected failure, which has to be attributed to the obviously substantially lower acidity of the β-protons at the furan nucleus as compared to those of the thiophene analogue, prompted us to search for a more powerful metalating agent. The best results were obtained with superbasic reagents of the *LIDAKOR*-type [13, 14] (mixtures of alkyllithium compounds, amines and potassium alcoholates). The more frequently used *LICKOR*-reagents [15] (superbases from alkyllithium and alcoholates only) are not applicable in our case due to their ability for halogen metal exchange.

A superbasic reagent prepared from *LDA* and potassium *tert.*-butanolate proved to be sufficient powerful for the metalation of **1**, and reaction conditions were developed which allowed the selective formation of the "rearranged" intermediate 2-lithio-3-bromo-5-methylfuran: **1** was rapidly added to freshly prepared *LIDAKOR* to provoke the bromine scrambling reaction of $\mathbf{L}_1$ to $\mathbf{L}_2$ *via* initial lithiation and formation of 2,3-dibromo-5-methylfuran as transhalogenation



Scheme 2

Table 1

Compd.	Electrophile	*E*	Yield (%)
2	CH_3I	$-CH_3$	29
3	$CH_3(CH_2)_3I$	$-(CH_2)_3CH_3$	28
4	$(CH_3)_3SiCl$	$Si(CH_3)_3$	44
5			32
6			42
7	$HCON(CH_3)_2$	$-CHO$	30
8	BrCN	$-Br$	31

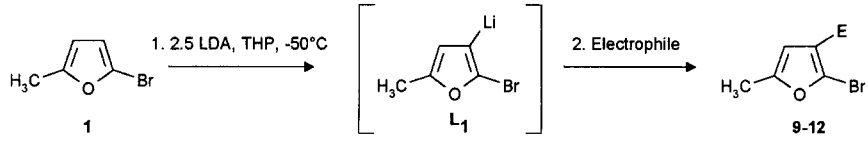
catalyst (Scheme 2). Subsequent quenching with various electrophiles revealed 2-substituted 3-bromo-5-methylfurans. No HD-retained isomers could be detected by NMR-spectroscopy of the crude reaction mixtures. After purification, the trisubstituted furan derivatives **2**–**8** were obtained in moderate yields (Table 1).

In spite of performing thorough investigations and numerous experiments under variation of reaction times and temperatures, the yields could not be improved (see below).

Prevention of halogen migration

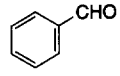
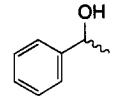
From own experience in this field [12], slow addition of starting material to excess of metalation base proved to be the method of choice to retain the substitution pattern, thus supplying conditions for a rapid removal of the aryl bromide to avoid subsequent transmetalation and scrambling reactions. With 2-bromo-5-methylfuran as substrate, neither *LDA/THF* (no metalation at all) nor *LIDAKOR/THF* (halogen dance due to slow initial metalation) were applicable. Changing the solvent to *THP* – already successfully introduced for migration/prevention control at dibromofurans [12] – was required. Upon slow addition of **1** to 2.5 equivalents of *LDA* in *THP* at $-50\,^{\circ}C$, no migration at all was observed (Scheme 3), and after quenching of $\mathbf{L}_1$ with various electrophiles and workup the corresponding 3-substituted

2-bromo-5-methylfurans **9**–**12** were obtained without any HD isomers detectable by NMR spectroscopy (Table 2). As for the migration products reported above, again moderate yields were obtained which could not be substantially increased by variation of reaction parameters (see below).



Scheme 3

Table 2

Compd.	Electrophile	*E*	Yield (%)
9	$(CH_3)_3SiCl$	$Si(CH_3)_3$	66
10			32
11			40
12	$HCON(CH_3)_2$	–CHO	26

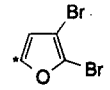
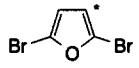
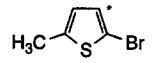
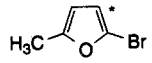
Discussion

Successful halogen migrations and preventions with unsymmetrically 2,5-disubstituted furans or thiophenes can be achieved only *via* the very crucial precondition of exclusive regioselective metalation at one of the β-hydrogens. As a matter of fact, opposite inductive and/or mesomeric properties of the substituents at the α-positions are required, as is true for 2-bromo-5-methylthiophene [11] and for 2-bromo-5-methylfuran (**1**).

Although the acidities of the hydrogens at the furan and the thiophene system are substantially different (Table 3), as can be deduced from the necessity to provide differently powerful metalation conditions, the initial lithiation – if providing appropriate reaction parameters (Table 3) – occurs at both substrates exclusively adjacent to the bromine substituent due to the electron withdrawing effect of the bromine atom in combination with the +I-effect of the methyl group.

The decrease of acidities affects position 3 of **1** – as compared to 2,5-dibromofuran [12] – to an extent that enforces the use of the superbasic reagent *LIDAKOR* to enable initial lithiation which could be accomplished only if allowing the reaction temperature to reach −20 °C in *THF*. This required rather elevated temperature accounts for problems of decomposition, arising from the very limited stability of *LIDAKOR* in *THF* [20]; superbases have never been used before above −50 °C. Another factor decreasing the overall yields concerns decomposition

Table 3. Investigation of Metalation Conditions. – : Not investigated or no selectivity; N.R.: no reaction; H: halogen dance; P: prevention of halogen dance

Substrate (*: Metalation Position)	Metalation Conditions		
	LDA/THF	*LDA/THP*	*LIDAKOR/THF*
	H/P [12]	P [12]	–
	H [12]	P [12]	–
	H [11]	–	H
	N.R.	P	H

reactions of the rearranged intermediary $\mathbf{L}_2$ prior to quenching with electrophiles. This might be due to the participation of solvent sensitive potassium organyls during the transmetalation steps involved in the scrambling sequence. It has been shown by ^{133}Cs-^{1}H HOESY NMR spectroscopy (Cs being preferred over K for its advantageous NMR properties) that metalation with superbases leads to incorporation of metal from Caesium-*t*-butoxide into organometallic species [19]. Moreover, these decompositions, caused by the basic properties of $\mathbf{L}_2$, compete with the quenching reactions in so far as the intermediate $\mathbf{L}_2$ shows weaker nucleophilicity as might have been expected from migrations at dibromofurans [12]: prolonged reaction times and elevated temperatures after addition of electrophiles were required, and the crude reaction mixtures always contained some amount of 4-bromo-2-methylfuran (generated from $\mathbf{L}_2$ decomposed *via* solvent, or from unreacted $\mathbf{L}_2$ hydrolyzed during work-up). The fact that stronger and rapidly reacting electrophiles (as benzaldehyde and *TMS*-Cl, cf. Tables 1 and 2) gave significantly better yields accompanied by less 4-bromo-2-methylfuran (=hydrolized $\mathbf{L}_2$) is an additional hint for the above mentioned suggestions.

Prevention of halogen dance at **1** required another variation of reaction conditions. It was by no means possible to retain the rearrangement, even by very slow addition of **1** to *LIDAKOR/THF*. Based on our experience from recently published work [8, 12], where we found *THP* to be an excellent metalation promoting solvent, *LDA/THP* again turned out to be the combination of choice which enabled the initial lithiation of **1** without consecutive scrambling reactions. However, 2.5 equ. of *LDA* proved to be necessary which again is accounting for the rather weak acidity of the *β*-hydrogens of **1**. Upon quenching with various electrophiles *E*, the crude reaction mixtures contained trisubstituted target furans with a 3-*E* 2-bromo "HD-prevention" pattern, no rearranged isomers, and substantial amounts of starting material **1** (which – removed by bulb-to-bulb distillation – was mainly responsible for the moderate yields obtained). In analogy to the migration reactions discussed

above, **1** recovered from HD-prevention reactions has to be mainly attributed to hydrolysis of $\mathbf{L}_1$ left after the addition of the electrophile due to its decreased nucleophilic properties (cf. Table 2: reactive "rapid" electrophiles such as *TMS*-Cl and benzaldehyde gave higher yields, accompanied by less 2-bromo-5-methylfuran **1**). The yield/reactivity ratio for the electrophiles employed (Tables 1 and 2) is in agreement with our observations and classification by "rapid" and "slow" electrophiles recently published in the area of dibromofurans [8, 12]. Moreover, the fact that no bromine scrambling is induced *via* concomitant presence of $\mathbf{L}_1$ and 3-*E*-substituted 2-bromo-5-methylfurans in the quenched reaction mixtures (which could be observed *via* occurrence of transmetalations (=halogen-metal exchanges) for HD-prevention reactions in the dibromofuran area applying certain "slow" electrophiles [8, 12]) is another indication for the decreased nucleophilic reactivity of lithio intermediary $\mathbf{L}_1$.

Conclusions

Starting from 2-bromo-5-methylfuran (**1**), a series of new trisubstituted derivatives was obtained. Due to the low acidity of the β-hydrogens of **1**, powerful metalation conditions had to be employed. *LIDAKOR/THF* led to an aryl bromide catalyzed dance (ABCD) reaction resulting in formation of 2-substituted 3-bromo-5-methylfurans **2**–**8**, whereas selective prevention of bromine migration provides another example for utilizing *THP* as metalation solvent: *LDA/THP* gave access to 3-substituted 2-bromo-5-methylfurans **9**–**12**. Within an ongoing research project, the synthetic applicability of the target compounds thus obtained for cross couplings, *Heck* reaction, metal-halogen exchange, and ring opening reactions is currently under investigation.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer (*TMS* as internal standard, $CDCl_3$, δ in ppm, J in Hz).

Starting material **1** has been mentioned in once literature [16], but neither a preparation procedure nor any physical or spectroscopic data can be found. In consequence, a procedure for the synthesis had to be developed. Compound **8** is also cited only once without any data [17].

Diisopropylamine was distilled twice over KOH and once over BuLi. Tetrahydrofuran (*THF*, pre-dried over potassium hydroxide) and tetrahydropyran (*THP*) were distilled from sodium/ benzophenone before use.

2-Bromo-5-methylfuran (**1**, C_5H_5BrO)

1 was prepared using the bromination procedure by *Brandsma* [18]. A solution of bromine (15.8 g, 98.8 mmol) in anhydrous *DMF* (40 ml), prepared by cooling the solvent below 0 °C and adding the bromine cautiously, was added to a solution of 2-methylfuran (8.1 g, 98.6 mmol) in 30 ml of anhydrous *DMF* over a period of 30 min at ambient temperature and stirred for further 30 min. The mixture was then poured onto ice, shaken vigorously for several minutes, and extracted with pentane. The combined organic layers were washed with saturated NaCl-solution twice and dried. After evaporation of the solvent and addition of 3 ml of N,N-diethylaniline, the product was distilled under reduced pressure.

Yield: 36%; b.p.: 51–54 °C / 45 mm; ^{1}H NMR: 6.16 (dq, 1H, H-3, J_{34} = 3.1 Hz, J_{3,CH_3} = 0.4 Hz), 5.95 (dq, 1H, H-4, J_{4,CH_3} = 1.1 Hz), 2.28 (dd, 3H, CH_3); ^{13}C NMR: 154.0 (s, C-5), 118.7 (s, C-2), 111.7 (d, C-3), 108.2 (d, C-4), 13.5 (q, CH_3).

General Procedure **A** – *Halogen Migration*

Diisopropylamine (0.76 g, 7.5 mmol) was dissolved in 30 ml of anhydrous *THF* and added to potassium *tert*-butanolate (0.84 g, 7.5 mmol) under nitrogen. The mixture was cooled to −80 °C, *n*-butyllithium (7.5 mmol) was added, and stirring was continued for 30 min. 2-Bromo-5-methylfuran (1 g, 6.2 mmol), dissolved in 10 ml of anhydrous *THF*, was added quickly and the temperature was allowed to reach −20 °C. Stirring was continued at this temperature for 90 min. The electrophile (10 mmol), dissolved in 10 ml of anhydrous *THF*, was added. The reaction mixture was then allowed to reach ambient temperature, stirred for further 30 minutes, poured on water and extracted with ether. The combined organic layers were dried and concentrated and the product purified by bulb-to-bulb distillation.

3-Bromo-2,5-dimethylfuran (**2**, C_6H_7BrO)

Yield: 29%; b.p.: 65–68 °C / 40 mm; ^{1}H NMR: 5.92 (m, 1H, H-4), 2.22 (m, 6H); ^{13}C NMR: 150.3 (s, C-5), 147.2 (s, C-2), 109.2 (d, C-4), 96.1 (s, C-3), 13.4 (q, 5-CH_3), 11.5 (q, 2-CH_3).

3-Bromo-2-butyl-5-methylfuran (**3**, $C_9H_{13}BrO$)

Yield: 28%; b.p.: 80–83 °C / 12 mm; ^{1}H NMR: 5.93 (q, 1H, H-4, J_{4,CH_3} = 1.0 Hz), 2.60 (t, 2H), 2.26 (d, 3H), 1.70–1.50 (m, 2H), 1.40–1.25 (m, 2H), 0.97 (t, 3H); ^{13}C NMR: 151.1 (s, C-2), 150.2 (s, C-5), 109.0 (d, C-4), 95.7 (s, C-3), 29.9 (t), 25.6 (t), 22.0 (t), 13.6 (q), 13.4 (q).

(3-Bromo-5-methyl-2-furanyl)-trimethylsilane (**4**, $C_8H_{13}BrOSi$)

Yield: 44%; b.p.: 60–63 °C / 12 mm; ^{1}H NMR: 6.03 (q, 1H, H-4, J_{4,CH_3} = 0.9 Hz), 2.29 (d, 3H, CH_3), 0.32 (s, 9H, Si–CH_3); ^{13}C NMR: 156.4 (s, C-5), 154.2 (s, C-2), 110.6 (s, C-3), 110.0 (d, C-4), 13.5 (q, CH_3), −1.7 (q, Si–CH_3).

1-(3-Bromo-5-methyl-2-furanyl)-cyclohexanol (**5**, $C_{11}H_{15}BrO_2$)

Yield: 32%; b.p.: 100–103 °C / 0.05 mm; ^{1}H NMR: 5.96 (q, 1H, H-4, J_{4,CH_3} = 1.0 Hz), 2.24 (d, 3H, CH_3), 2.15–1.20 (m, 10H); ^{13}C NMR: 152.5 (s, C-2′), 150.2 (s, C-5′), 111.1 (d, C-4′), 94.3 (s, C-3′), 71.5 (s, C-1), 36.2 (t, C-2, C-6), 25.2 (t, C-4), 21.9 (t, C-3, C-5), 13.3 (q, CH_3).

3-Bromo-5-methyl-α-phenyl-2-furanmethanol (**6**, $C_{12}H_{11}BrO_2$)

Yield: 42%; b.p.: 80–82 °C / 0.01 mm; ^{1}H NMR: 7.50–7.30 (m, 5H), 6.01 (q, 1H, H-4, J_{4,CH_3} = 1.0 Hz), 5.92 (s, 1H, H-α), 2.24 (d, 3H, CH_3); ^{13}C NMR: 152.6 (s, C-5), 149.4 (s, C-2), 140.4 (s, C-1′), 128.3 (d, C-3′, C-5′), 127.7 (d, C-4′), 126.1 (d, C-2′, C-6′), 109.6 (d, C-4), 98.0 (s, C-3), 67.6 (d, C-α), 13.5 (q, CH_3).

3-Bromo-5-methyl-2-furancarbaldehyde (**7**, $C_6H_5BrO_2$)

Yield: 30%; m.p.: 85–86 °C; ^{1}H NMR: 9.60 (s, 1H, CHO), 6.31 (q, 1H, H-4, J_{4,CH_3} = 0.8 Hz), 2.41 (d, 3H, CH_3); ^{13}C NMR: 175.2 (d, CHO), 159.5 (s, C-5), 147.0 (s, C-2), 114.3 (s, C-3), 113.1 (d, C-4), 14.0 (q, CH_3).

2,3-Dibromo-5-methylfuran (**8**, $C_5H_4Br_2O$)

Yield: 31%; b.p.: 80–83 °C / 12 mm; ^{1}H NMR: 6.07 (q, 1H, H-4, J_{4,CH_3} = 1.1 Hz), 2.28 (d, 3H, CH_3); ^{13}C NMR: 154.5 (s, C-5), 119.8 (s, C-2), 111.3 (d, C-4), 101.7 (s, C-3), 13.8 (q, CH_3).

General Procedure **B** – *HD-Prevention*

Diisopropylamine (1.57 g, 15.5 mmol) was dissolved in 30 ml of anhydrous tetrahydropyran under nitrogen and cooled to −50 °C. *n*-Butyllithium (15.5 mmol) was added and the mixture was stirred for 20 min. 2-Bromo-5-methylfuran (1 g, 6.2 mmol), dissolved in 20 ml of anhydrous tetrahydropyran, was added dropwise over a period of 75 min, and stirring was continued at −50 °C for 90 min. The electrophile (20 mmol), dissolved in 10 ml of anhydrous tetrahydropyran, was added maintaining the temperature at −50 °C. The reaction mixture was then stirred for another 30 min, poured onto water and extracted with ether. The combined organic layers were dried and concentrated and the product purified by bulb-to-bulb distillation.

(2-Bromo-5-methyl-3-furanyl)-trimethylsilane (**9**, $C_8H_{13}BrOSi$)

Yield: 66%; b.p.: 77–80 °C / 12 mm; ^{1}H NMR: 5.91 (q, 1H, H-4, J_{4,CH_3} = 1.0 Hz), 2.27 (d, 3H, CH_3), 0.24 (s, 9H, Si–CH_3); ^{13}C NMR: 153.7 (s, C-5), 123.8 (s, C-2), 118.8 (s, C-3), 112.2 (d, C-4), 13.2 (q, CH_3), −1.4 (q, Si–CH_3).

1-(2-Bromo-5-methyl-3-furanyl)-cyclohexanol (**10**, $C_{11}H_{15}BrO_2$)

Yield: 32%; b.p.: 82–85 °C / 0.03 mm; ^{1}H NMR: 6.03 (q, 1H, H-4, J_{4,CH_3} = 1.0 Hz), 2.24 (d, 3H, CH_3), 2.00–1.10 (m, 10H); ^{13}C NMR: 152.6 (s, C-5′), 131.3 (s, C-3′), 113.8 (s, C-2′), 107.5 (d, C-4′), 69.3 (s, C-1), 37.1 (t, C-2, C-6), 25.2 (t, C-4), 21.6 (t, C-3, C-5), 13.4 (q, CH_3).

2-Bromo-5-methyl-α-phenyl-3-furanmethanol (**11**, $C_{12}H_{11}BrO_2$)

Yield: 40%; b.p.: 114–117 °C / 0.03 mm; ^{1}H NMR: 7.45–7.30 (m, 5H), 5.98 (q, 1H, H-4, J_{4,CH_3} = 1.1 Hz), 5.72 (s, 1H, H-α), 2.25 (d, 3H, CH_3); ^{13}C NMR: 154.2 (s, C-5), 142.4 (s, C-1′), 128.3 (d, C-3′, C-5′), 127.5 (d, C-4′), 127.2 (s, C-3), 125.7 (d, C-2′, C-6′), 117.1 (s, C-2), 106.9 (d, C-4), 68.5 (d, C-α), 13.7 (q, CH_3).

2-Bromo-5-methyl-3-furancarbaldehyde (**12**, $C_6H_5BrO_2$)

Yield: 26%; b.p.: 62–65 °C / 0.03 mm; ^{1}H NMR: 9.73 (d, 1H, CHO, $J_{4,CHO}$ = 0.4 Hz), 6.36 (dq, 1H, H-4, J_{4,CH_3} = 1.1 Hz), 2.31 (d, 3H, CH_3); ^{13}C NMR: 184.3 (d, CHO), 156.2 (s, C-5), 131.1 (s, C-2), 125.6 (s, C-3), 105.3 (d, C-4), 13.6 (q, CH_3).

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