Trapping of Diacceptor-Substituted Methylenecyclopropanes with Isocyanides – A Further Application of the Principle of the Twofold Nucleophilic Substitution at a Cyclopropane

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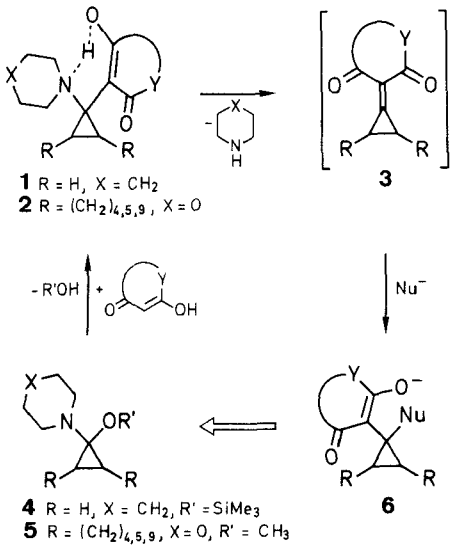
Dedicated to Prof. Dr. H.J. Bestmann on the occasion of his 65th birthday

Unstable 2-cyclopropylidene-1,3-diones **3** can be trapped by isocyanides **8** to give [4+1]-cycloadducts **9** and **12**. In the case of Meldrum's acid, as the dioxo component, spirotricyclic imides **15** are isolated due to an easy degradation of the primary cycloaddition products **14** in methanol. Subsequent reactions are described for the [4 + 1]cycloadducts leading to a cyclopropanecarboxamide **19b** or to a phenylamino-substituted furan **20/21**. Trapping of **3** by isocyanides **8** represents a novel second step in the concept of the twofold nucleophilic substitution at a cyclopropane.

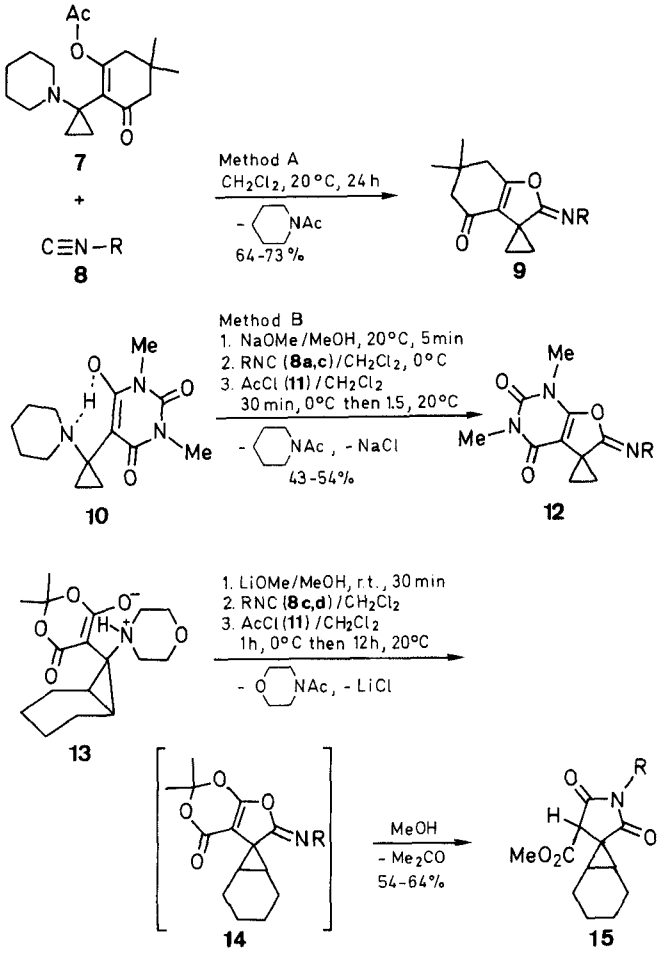
2-Cyclopropylidene-1,3-cycloalkanediones **3** represent a class of very reactive compounds which as yet have proved to be unisolable.[1] They are trapped, however, by a variety of reagents such as 1,3-dienes,[2] electron-rich alkenes,[3] electron-rich alkynes,[4] or nucleophiles (e.g. cyanide,[5] hydride,[5] amines,[6] carbanions[7–11]). leading to products **6**. Intermediates **3** are best generated from aminocyclopropylated CH-acids **1/2**. Since the latter are easily prepared from cyclopropanone *O,N*-acetals **4/5** and CH-acids, the sequence **4/5** → **1/2** → **6** corresponds to the overall result of a twofold nucleophilic substitution at a cyclopropane.



[4 + 1]-Cycloaddition reactions are reported to take place between isocyanides and a few α,β-unsaturated ketones.[12–16] Thereby the α,β-unsaturated ketone either has to be activated by a further acceptor moiety (e.g. a $-CF_3$,[14] or a C=O[15,16] group) or diethylaluminum chloride is necessary as a catalyst.[13] Our present investigations show that 2-cyclopropylidene-1,3-cycloalkanediones **3** are activated enough to be trapped by isocyanides **8** smoothly, in situ, using mild reaction conditions.

Thus [4 + 1]-cycloaddition products **9a–c** are obtained in 64–73% yield from an isocyanide **8** and the acylated dimedone derivative **7** after 24 h at room temperature in dichloromethane as a solvent. The generation and the trapping of 5-cyclopropylidenebarbituric acid **3** is managed by addition of acetyl chloride to a suspension of the sodium salt of **10** and an isonitrile **8**. Compounds **12a** and **12c** were isolated in 43% and 54% yield, respectively. A similar procedure is applied to the bicyclic Meldrum's acid derivative **13** using its lithium salt. Here, however, the [4 + 1]-cycloaddition product **14** decomposes very easily to give a stable methyl ester **15** upon addition of methanol (overall yields: **15c**: 54%; **15d**: 64%). The degradation of the Meldrum's acid moiety in **14** is accompanied by an acylimidate – imide rearrangement (example of a Dimroth rearrangement[17]).

The ^{13}C-NMR data clearly demonstrate the structure of the cycloadducts **9** and **12**, as well as the tricyclic imides **15**. The presence of a cyclopropane system is indicated by a singlet and one triplet in the case of **9** and **12**, and a



8,9,12,14,15	a	b	c	d
R	CH_2Ts	*t*-Bu	Ph	4-$MeOC_6H_4$

singlet and two doublets in the case of **15**. The $^1J_{CH}$ coupling constants are characteristic of a cyclopropane system (see Table 2 and the experimental). The imidate ^{13}C-NMR signal ranges from δ = 156.6 to 167.7 for **9a–c** and occur at δ = 157–158 for **12a** and δ = 163.8 for **12c**. In contrast, the signals for the enone system are almost constant for compounds **9** and **12**, respectively. This behavior is consistent with the imidate structure **9** and **12** and would not be expected for a lactam-type structure **16**. The *N*-phenyl substituent gives further proof for the imidate unit in **9c** and **12c**. The C-1 atom of the *N*-phenyl group shows absorption at δ = 144.8 for **9c** or δ = 143.4 for **12c**. This value is in accordance with literature data for an isocyanide – [4 + 1]cycloadduct (imidate – struc-

Table 1. ^{1}H-NMR Spectroscopic Data of Compounds **9** and **12** ($CDCl_3$/TMS, δ)

Compound	Cyclopropane (m_c)[a]	Bicyclic System		R
		CH_3 (s)	CH_2 (s)[a]	
9a	1.27, 1.79	1.12[b]	2.22, 2.43	2.43 (s, 3H), 4.73 (s, 2H), 7.34, 7.78 (AA'XX'-system, 4H)
9b	1.10, 1.66	1.15[b]	2.23, 2.49	1.26 (s, 9H)
9c	1.46, 1.91	1.14[b]	2.27, 2.49	7.11 (m_c, 3H), 7.32 (m_c, 2H)
12a	1.32, 1.85	3.30[c], 3.43[c]	–	2.46 (s, 3H), 4.76 (s, 2H), 7.36, 7.79 (AA'XX'-system, 4H)
12c	1.52, 1.92	3.31[c], 3.38[c]	–	7.12 (m_c, 3H), 7.34 (m_c, 2H)

[a] Each signal corresponds to 2H.
[b] 6H.
[c] 3H.

Table 2. ^{13}C-NMR Spectroscopic Data of Compounds **9** and **12** ($CDCl_3$/TMS, δ)

Compound	Cyclopropane		Condensed Bicyclic System						R
	(s)	(t)[a]	Enone (s)	(s)	O–C=N (s)	CH_3 (q)	CH_2 (t)	C_q (s)	
9a	24.7	17.7 [167]	169.0, 192.7	116.1	167.7	28.5	36.7, 51.2	34.1	21.5 (q), 68.0 (t), 128.9 (d), 129.3 (d), 134.4 (s), 144.6 (s)
9b	24.2	16.6 [166]	169.9, 192.7	115.3	156.6	28.7	37.3, 51.3	33.9	30.0 (q), 53.6 (s)
9c	24.9	17.7 [165]	169.7, 192.7	115.8	161.5	28.5	37.0, 51.3	34.0	122.6 (d), 124.1 (d), 128.5 (d), 144.8 (s)
12a	24.9	16.5 [166]	157.8[b], 156.6[b], 150.6	89.6	163.8[b]	27.6, 29.5	–	–	21.4 (q), 68.5 (t), 129.0 (d), 129.6 (d), 134.3 (s), 145.2 (s)
12c	25.1	16.7 [167]	157.9[b], 157.0[b], 150.7	89.6	157.3[b]	27.7, 29.7	–	–	122.7 (d), 125.0 (d), 128.9 (d), 143.4 (s)

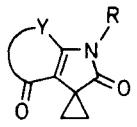
[a] $^1J_{CH}$ coupling constant (Hz) in [parenthesis].
[b] Unequivocal assignment not possible.

Table 3. Products **9** and **12** from the Cycloaddition of Isocyanides **8** with 2-Cyclopropylidene-1,3-cycloakanediones **3** (R = H)

Product	Method	Recrystallization Solvent	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR (KBr) $\nu_{C=O}$, $\nu_{C=N}$, $\nu_{C=C}$ (cm^{-1})
9a	A	acetone/H_2O (1:1)	0.60 g (64%)	135	$C_{20}H_{23}NO_4S$ (373.5)	1715, 1665, 1595
9b	A	acetone/H_2O (1:1)	0.48 g (73%)	96	$C_{16}H_{23}NO_2$ (261.4)	1730, 1655, 1635
9c	A	MeOH[c]	0.49 g (70%)	112	$C_{18}H_{19}NO_2$ (281.4)	1700, 1650, 1585
12a	B	MeCN	0.42 g (43%)	183	$C_{18}H_{19}N_3O_5S$ (389.4)	1740, 1700–1670 (br), 1645, 1590
12c	B	MeOH	0.40 g (54%)	170	$C_{16}H_{15}N_3O_3$ (297.3)	1740, 1700, 1665 (br), 1590

[a] Yield of isolated product **9** and **12** based on **7** and **10** as starting material, respectively.
[b] Satisfactory microanalyses obtained: C ±0.37, H ±0.22, N ±0.29.
[c] The filtrate from the crystallization is concentrated and the solid is recrystallized from MeOH/H_2O (1:1).

ture[15]). Furthermore, it fits very well with the analogous signal of imidate **17** (δ = 145.0[18]) and contrasts strongly with the *N*-phenyl *ipso*-C signal of imide **18** (δ = 131.3;[19] at least **9** can be regarded as a vinylogous imide compound). On the other hand, the absorption of the *N*-phenyl singlet (C-*ipso*) unequivocally establishes a phenyl–imide structure **15** which stems from an imino – imide rearrangement (**15c**: δ = 131.8, **15d**: δ = 124.4, an upfield shift of 7.7 ppm[20] with respect to **15c** is expected for this signal due to the OCH_3-group at the 4-position). Compounds **15c** and **15d** are formed as one pure isomer. The configuration of **15c** and **15d** is not clear, but according to other trapping experiments of bicycloheptylidene Meldrum's acid intermediate **3**, a 1α,6α,7α-structure is most likely.[1,2,5–7,11]



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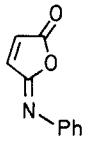

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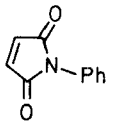

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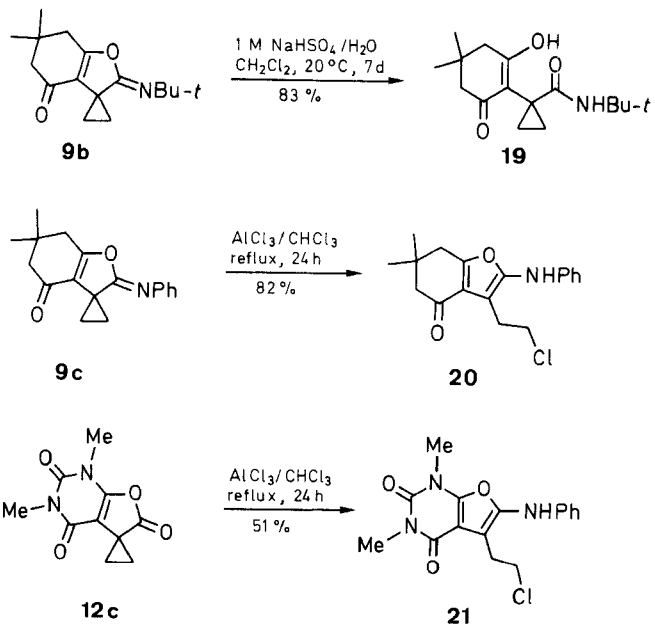
The isocyanide trapping products can be used for subsequent reactions. Thus hydrolysis of **9b** leads to a substituted cyclopropanecarboxamide **19** (83% yield). Aluminum chloride induced ring opening transfers the phenyl substituted cycloadducts **9a** and **12a** into the aminofuran derivatives **20** (82% yield) and **21** (51% yield), respectively. The structure of **20** and **21** can be deduced from the ^{13}C-NMR data: the high field shifting of the phenyl *ortho* and *para*-C-atoms (**20**: δ = 114.1 and 120.1; **21**: δ = 114.0 and 120.5) exclude an isomeric pyrrole unit in which interaction of the nitrogen lone pair and the phenyl unit is strongly decreased (*N*-phenylpyrrole:[21] phenyl-C-2/6 signals: δ = 126.1, phenyl-C-4 signal: δ = 127.8). The CH_2Cl-moiety is indicated by a triplet with a coupling constant characteristic of an adjacent chlorine substituent[22] (**20**: δ = 44.6, $^1J_{CH}$ = 153 Hz; **21**: δ = 44.0, $^1J_{CH}$ = 153 Hz). Addition of silver nitrate solution gives the information about the absence of ionic chloride; this is in accordance with the chloroethyl structural unit.



9b **19**

9c **20**

12c **21**

The trapping reactions of 2-cyclopropylidene-1,3-cycloalkanediones **3** with isocyanides **8** perform the connection of a d^1-carbon unit to a cyclopropane system. Thus, this sequence represents a further example for the application of the principle of twofold nucleophilic substitution at a cyclopropane.

All reagents were of commercial quality; CH_2Cl_2 and $CHCl_3$ were dried over Sicapent; TOSMIC is commercially available. The ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AM 400 spectrometer. The designation m_c is used to denote a complex multiplet. The IR spectra were measured on a Perkin-Elmer 397 Infrared Spectrophotometer. Microanalyses were performed with a Perkin-Elmer 2400 Elemental Analyzer.

Bicylic Imidates 9 and 12; General Procedure:

Method A *for Imidates* **9**: A solution of acylated dimedone derivative **7**[3] (0.76 g, 2.5 mmol) and isocyanide **8** (2.5 mmol; **8a**: 0.49 g, **8b**[23]: 0.21 g, **8c**[24]: 0.26 g) in CH_2Cl_2 is stirred at 20 °C for 24 h. Removal of the solvent *in vacuo* and crystallization of the residue gives crystalline imidates **9** (see Table 3.).

Method B *for Imidates* **12**: A solution of NaOMe in MeOH (2 M, 2.5 mL) is added to a suspension of aminocyclopropylated barbituric acid **10**[8] (1.40 g, 2.5 mmol) in MeOH (15 mL) and stirred for 5 min at 20 °C. The solvent is removed *in vacuo*. The residue is stirred in Et_2O (25 mL) for 24 h, then isolated by suction filtration, washed with Et_2O (2 × 20 mL) and dried *in vacuo*. A mixture of this salt, isocyanide **8** (2.5 mmol; **8a**: 0.49 g, **8c**:[24] 0.26 g) and CH_2Cl_2 (30 mL) is stirred at 0 °C. A solution of AcCl (**11**; 0.22 g, 2.75 mmol) in CH_2Cl_2 is slowly added over 30 min. Stirring is continued for 1.5 h at 20 °C. Filtration and evaporation of the solvent gives crude **12** which is recrystallized.

Methyl 1'-Aryl-2',5'-dioxospiro[bicyclo[4.1.0]heptane-7,3'-pyrrolidine]-4'-carboxylates 15: General Procedure:

Meldrum's acid derivative **13**[25] (0.65 g, 2.0 mmol) is added to a solution of LiOMe in MeOH (0.1 M LiOMe; 20 mL). Stirring for 30 min and removing the solvent *in vacuo* gives the crude lithium salt which is purified by trituration with Et_2O (30 mL) and washing with pentane (2 × 15 mL). A solution of AcCl (**11**; 0.14 mL, 2.0 mmol) in CH_2Cl_2 (20 mL) is added to a stirred mixture of dried lithium salt (12 h, 20 °C/0.01 mbar) and isocyanide **8** (2.0 mmol; **8c**:[24] 0.21 g; **8d**:[26] 0.27 g) in CH_2Cl_2 (40 mL) at 0 °C. Stirring is continued for 1 h at 0 °C and 12 h at 20 °C. Filtration and removal of the solvent *in vacuo* lead to an oil which gives a crystalline compound upon dissolving in MeOH (10 mL), addition of water till turbidity and storage at 4 °C for 24 h. Recrystallization from MeOH/H_2O yields pure products **15c** and **15d**.

Methyl 2',5'-Dioxo-1'-phenylspiro[bicyclo[4.1.0]heptane-7,3'-pyrrolidine]-4'-carboxylate (**15c**): Yield: 0.34 g (54%); mp 124 °C.

$C_{18}H_{19}NO_4$	calc.	C 69.00	H 6.11	N 4.47
(313.4)	found	68.4	6.1	4.3

IR (KBr): ν = 1770, 1730, 1700 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 1.04 (m_c, 1 H), 1.28 (m_c, 1 H), 1.41 (m_c, 4 H), 1.75 (m_c, 1 H), 1.91 (m_c, 1 H), 2.11 (m_c, 1 H), 2.22 (m_c, 1 H), 3.72 (s, 1 H), 3.80 (s, 3 H), 7.30–7.47 (m, 5 H).

^{13}C-NMR ($CDCl_3$): δ = 18.7 (t), 19.4 (t), 20.6 (t), 20.9 (t), 21.5 (d, $^1J_{CH}$ = 166 Hz), 25.2 (d, $^1J_{CH}$ = 166 Hz), 31.5 (s), 49.3 (d), 53.0 (q), 126.2 (d), 128.5 (d), 128.9 (d), 131.8 (s), 167.8 (s), 171.4 (s), 178.2 (s).

Methyl 1'-(4-Methoxyphenyl)-2',5'-dioxospiro[bicyclo[4.1.0]heptane-7,3'-pyrrolidine]-4'-carboxylate (**15d**): Yield: 0.44 g (64%); mp 154 °C.

$C_{19}H_{21}NO_5$	calc.	C 66.46	H 6.16	N 4.08
(343.4)	found	66.4	6.1	4.0

IR (KBr): ν = 1770, 1700 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 1.02 (m_c, 1 H), 1.25 (m_c, 1 H), 1.41 (m_c, 4 H), 1.72 (m_c, 1 H), 1.91 (m_c, 1 H), 2.09 (m_c, 1 H), 2.20 (m_c, 1 H), 3.70 (s, 1 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 6.95, 6.97 (2 H), 7.21, 7.23 (2 H) (AA'XX'-system).

^{13}C-NMR ($CDCl_3$): δ = 18.7 (t), 19.4 (t), 20.6 (t), 20.9 (t), 21.4 (d, $^1J_{CH}$ = 163 Hz), 25.1 (d, $^1J_{CH}$ = 165 Hz), 31.4 (s), 49.2 (d), 53,0 (q), 55.3 (q), 114.2 (d), 124.4 (s), 127.5 (d), 159.3 (s), 167.9 (s), 171.6 (s), 178.5 (s).

N-tert-Butyl-1-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)cyclopropanecarboxamide **(19)**:
A mixture of imidate **9b** (0.26 g, 1.0 mmol), aq $NaHSO_4$ solution (1 M, 25 mL) and CH_2Cl_2 (25 mL) is stirred at 20 °C for 7 d. The CH_2Cl_2 layer is separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). Evaporation of the CH_2Cl_2 gives crude **19** which is recrystallized from acetone/H_2O (1 : 1). Yield: 0.23 g (83 %), mp 134 °C.

$C_{16}H_{25}NO_3$	calc.	C 68.79	H 9.02	N 5.01
(279.4)	found	68.7	8.9	5.2

IR (KBr): ν = 3380 (OH), 1620, 1600 cm^{-1} (C=O, C=C).

^{1}H-NMR (CD_3ONa/CD_3OD solution, 0.5 M): δ = 0.65 (m_c, 2 H), 1.03 (s, 6 H), 1.15 (m_c, 2 H), 1.27 (s, 9 H), 2.19 (s, 4 H).

^{13}C-NMR (CD_3ONa/CD_3OD solution, 0.5 M): δ = 15.4 (t, $^1J_{CH}$ = 163 Hz), 23.5 (s), 29.16 (q), 29.19 (q), 32.8 (s), 51.1 (t), 51.5 (t), 111.8 (s), 177.9 (s), 194.5 (s).

Ring Opening Reactions of 9c and 12c; General Procedure:
A suspension of imidate **9c** (0.28 g, 1.0 mmol) or **12c** (0.30 g, 1.0 mmol) and $AlCl_3$ (0.13 g, 1.0 mmol) in $CHCl_3$ (20 mL) is refluxed for 24 h. Filtration and evaporation of the solvent gives crude **20** or **21** which are crystallizing upon the addition of cold MeOH.

3-(2-Chloroethyl)-6,7-dihydro-6,6-dimethyl-2-phenylamino-benzofuran-4(5H)-one **(20)**: Yield: 0.26 g (82 %); mp 123 °C.

$C_{18}H_{20}ClNO_2$	calc.	C 68.03	H 6.34	N 4.41
(317.8)	found	68.0	6.4	4.3

IR (KBr): ν = 1655, 1640, 1600, 1570 cm^{-1} (C=O, C=C).

^{1}H-NMR ($CDCl_3$): δ = 1.14 (s, 6 H), 2.37 (s, 2 H), 2.68 (s, 2 H), 2.99 (t, 2 H), 3.79 (t, 2 H), 5.69 (s, 1 H, NH), 6.69 (m_c, 2 H), 6.85 (m_c, 1 H), 7.20 (m_c, 2 H).

^{13}C-NMR ($CDCl_3$): δ = 27.0 (t), 28.5 (q), 34.9 (s), 37.2 (t), 44.6 (t), 52.2 (t), 110.5 (s), 114.1 (d), 119.0 (s), 120.1 (d), 129.2 (d), 144.6 (s), 146.7 (s), 162.9 (s), 194.4 (s).

5-(2-Chloroethyl)-1,3-dimethyl-6-phenylamino-furo[2,3-d]pyrimidine-2,4(1H,3H)-dione **(21)**: Yield: 0.17 g (51 %); mp 140 °C (dec).

$C_{16}H_{16}ClN_3O_3$	calc.	C 57.58	H 4.83	N 12.59
(333.8)	found	57.6	4.8	12.6

IR (KBr): ν = 1695, 1655, 1645, 1600, 1520 cm^{-1} (C=O, C=C).

^{1}H-NMR ($CDCl_3$): δ = 3.05 (t, 2 H), 3.40 (s, 3 H), 3.49 (s, 3 H), 3.91 (t, 2 H), 5.68 (s, 1 H, NH), 6.71 (m_c, 2 H), 6.90 (m_c, 1 H), 7.24 (m_c, 2 H).

^{13}C-NMR ($CDCl_3$): δ = 27.1 (t), 28.1 (q), 29.4 (q), 44.0 (t), 96.1 (s), 113.7 (s), 114.0 (d), 120.5 (d), 129.4 (d), 143.0 (s), 144.3 (s), 150.6 (s), 152.6 (s), 158.5 (s).

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