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Ring Contraction of 2-Chlorocyclohexanone with Grignard Reagents

MIKIO HORI,* TADASHI KATAOKA, HIROSHI SHIMIZU, EIJI IMAI,
TATSUNORI IWAMURA, and KAORI MAEDA

*Gifu Pharmaceutical University, 6–1, Mitahora-higashi
5-chome, Gifu 502, Japan*

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The reaction of 2-chlorocyclohexanone with phenylmagnesium bromide in refluxing tetrahydrofuran unexpectedly afforded the ring-contracted product, cyclopentyl phenyl ketone, as the main product in moderate yield. The reactivities of several cyclic 2-haloketones were examined.

Keywords——2-chlorocyclohexanone; Grignard reaction; ring contraction; cyclopentyl phenyl ketone; solvent effect; THF; conformational isomer

The reaction of 2-chlorocyclohexanone (**1**) with Grignard reagents is a widely used synthetic method for 2-alkyl- and 2-arylcyclohexanones.[1] 2-Phenylcyclohexanone (**3**) can be obtained by the reaction of **1** with phenylmagnesium bromide in refluxing benzene.[1c] It is known that the reaction of **1** with phenylmagnesium bromide affords the intermediary magnesium salt (**2**) of the chlorohydrin, which forms **3** by the thermal rearrangement of the phenyl group, and a small amoutnt of **4** by the migration of a methylene group (Chart 1).[1d]

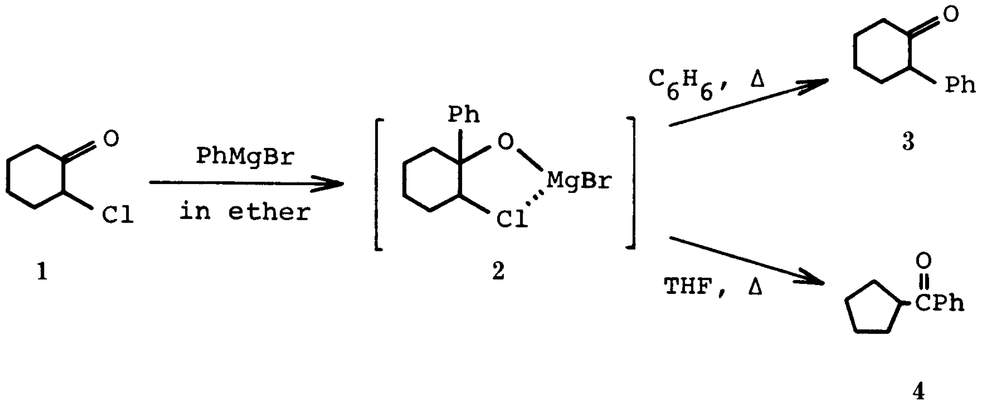


Chart 1

However, when we examined the reaction in refluxing tetrahydrofuran (THF) instead of benzene, ring contraction took place, affording cyclopentyl phenyl ketone (**4**) as the major product. We therefore investigated this unusual reaction in detail.

Results

The haloketone **1** was allowed to react with phenylmagnesium bromide in ether and then the reaction mixture was heated in benzene or THF with various ratios of phenylmagnesium bromide to **1** (1.0, 1.2, 1.5 and 2.0 eq). The main product was **3** in benzene but **4** in THF, regardless of the amount of the Grignard reagent (Table I). No change in the ratio of **3** to **4**

Table I. Reaction of **1** with PhMgBr

	Molar ratio of PhMgBr to **1**	Yields (%)	
		3	**4**
In C_6H_6	1.0	49	—
	1.2	55	<2
	1.5	46	—
	2.0	39	—
	1.2 (TMEDA)	52	<2
In THF	1.0	10	40
	1.2	5	44
	1.5	6	42
	2.0	5	37
	1.2 (TMEDA)	5	45

Table II. Solvent Effects in the Reaction of **1** with PhMgBr

Solvent A	Solvent B	Temp.	Yields (%)	
			3	**4**
Ether	C_6H_6	Reflux	55	Trace (<2)
Ether	C_6H_6	65±2 °C	49	Trace
Ether	DME	Reflux	26	17
Ether	THF	Reflux	5	44
Ether–THF	THF	Reflux	Trace	47
THF	THF	Reflux	0—10	40—51
Ether	Dioxane	Reflux	Trace	28
Dioxane	Dioxane	Reflux	Trace	26

$$\mathbf{1} \xrightarrow[\text{2) solvent B, temp., 12 h}]{\text{1) 1.2 eq PhMgBr/solvent A, r.t., 2 h}} \mathbf{3}+\mathbf{4}$$

was observed in the presence of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA).

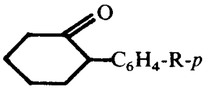
Solvent effects were examined using benzene, dioxane, dimethoxyethane (DME) and THF (Table II). As regards the effect of the reaction temperature, the thermolysis of **2** in benzene at 65±2 °C afforded **3** in 49% yield and a trace amount of **4**. The pyrolysis of **2** in refluxing DME (bp 83 °C) gave **3** and **4** in 26% and 17% yields, respectively. Thermolysis of **2** in THF gave **3** and **4** in 5% and 44% yields, respectively. In refluxing dioxane, **4** was obtained in 28% yield together with a trace amount of **3**. The rearrangement of **2** to **4** was thus promoted in cyclic ethers (THF, dioxane). Consequently, the reaction temperature may not affect the ratio of **3** to **4** as much as the polarity of the solvents and the solubility of **2** in them.

The reactions of **1** with aryl Grignard reagents were examined (Table III). The results with diphenylmagnesium were similar to those with phenylmagnesium bromide. The aryl group rearranged in refluxing benzene to produce the 2-substituted cyclohexanones (**3**, **5**, **7**) mainly. On the other hand, the ring-contracted products (**4**, **6**, **8**) were obtained predominantly when THF was used. Bachmann *et al.*[1f)] and Huang[1g)] reported that the reaction of **1** with *p*-methoxyphenylmagnesium bromide in ether gave only 2-(*p*-methoxyphenyl)-cyclohexanone (**9**) without heating because of the ease of migration of the *p*-methoxyphenyl group. This was confirmed in our experiment.

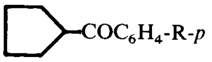
The rearrangements of several cyclic 2-haloketones with Grignard reagents were investigated (Table IV). 2-Chloro-2-methylcyclohexanone (**12**) underwent ring contraction in

Table III. Reaction of **1** with Aryl Grignard Reagents

p-R-C_6H_4MgX		Solvent	Products (Yields %)	
R	X		A	B
H	Ph	C_6H_6	**3** (52)	**4** (<5)
H	Ph	THF	**3** (<3)	**4** (49)
Me	Br	C_6H_6	**5** (53)	**6** (<3)
Me	Br	THF	**5** (12)	**6** (39)
Cl	Br	C_6H_6	**7** (50)	**8** (<3)
Cl	Br	THF	**7** (4)	**8** (46)
MeO	Br	Ether	**9** (52)	—

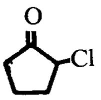
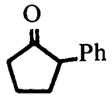
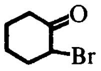
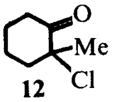
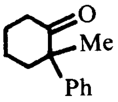
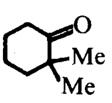
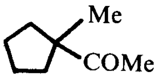
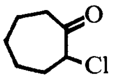
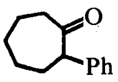
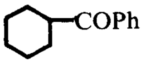
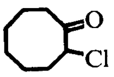
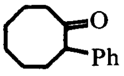


B



A

Table IV. Reactions of Cyclic 2-Haloketones with Grignard Reagents

2-Haloketone	Reagent	Solvent	Products (Yields %)	
 **10**	PhMgBr	THF	 **15** (18)	
 **11**	PhMgBr	THF	**3** (46)	**4** (6)
 **12**	PhMgBr	C_6H_6	 **16** (57)	 **17** (4)
12	PhMgBr	THF	**16** (37)	**17** (11)
12	MeMgI	C_6H_6	 **18** (47)[a]	 **19** (11)[a]
12	MeMgI	THF	**18** (37)[a]	**19** (21)[a]
 **13**	PhMgBr	C_6H_6	 **20** (28)	
13	PhMgBr	THF	**20** (21)	 **21** (10)
 **14**	PhMgBr	THF	 **22** (31)	

a) Yields were determined from the NMR spectra.

THF to give 1-methylcyclopentyl phenyl ketone (**17**) or methyl 1-methylcyclopentyl ketone (**19**) in 11% or 21% yield, respectively. 2-Chlorocycloheptanone (**13**) also gave a ring-contracted product, cyclohexyl phenyl ketone (**21**), in 10% yield. In these cases, however, the major products were the rearranged 2-substituted cycloketones (**16**, **18**, **20**) rather than the ring-contracted products. On the other hand, 2-chlorocyclopentanone (**10**) and 2-chlorocyclooctanone (**14**) produced no ring-contracted products but only 2-phenylketones, even in THF. It is interesting that 2-bromocyclohexanone (**11**) afforded mainly an ordinarily rearranged product **3** even in THF, in contrast to **1**.

Discussion

Stereochemical studies of the rearrangement of the magnesium salts of halohydrins to ketones have demonstrated that the halo and hydroxyl groups must be *cis* for the rearrangement to occur.[1d] As shown in Chart 2, the Grignard reagent should attack C-1 of **23e** solely from the equatorial side to produce the intermediate **25** in which the arrangement of halo and methylene groups is antiperiplanar. Then the C-6 methylene group attacks the C-2 carbon bound to the halogen atom by an S_N2 mechanism to yield **4**. The five-membered ring transition state of **25** might accelerate the ring contraction. In the other conformer **23a**, the Grignard reagent attacks the carbonyl group from the axial side to give an intermediate **24** which undergoes phenyl migration to form the product **3**.

The ratio of isomers **23a** and **23e** is not correlated to that of products **3** and **4**. The difference might be explained as described below. Allinger *et al.*[2] reported that the chlorine atom of **1** preferentially occupied the equatorial position (**23e**) rather than the axial position (**23a**) in polar solvents such as dioxane. On the basis of Allinger's discussion of the conformers **23a** and **23e**, we assume that dipole repulsion between chlorine and oxygen of **25** is reduced in polar solvents and intermediate **25** would be more stable than **24** in THF. Therefore, **24** isomerizes to **25** and forms **4**. On the other hand, in non-polar solvents such as benzene, **25** would isomerize to **24** and give **3**.

In the case of 2-bromocyclohexanone (**11**), the bromo group exists preferentially in the axial conformation (**23a**).[3] Thus the Grignard reagent attacks the carbonyl group from the

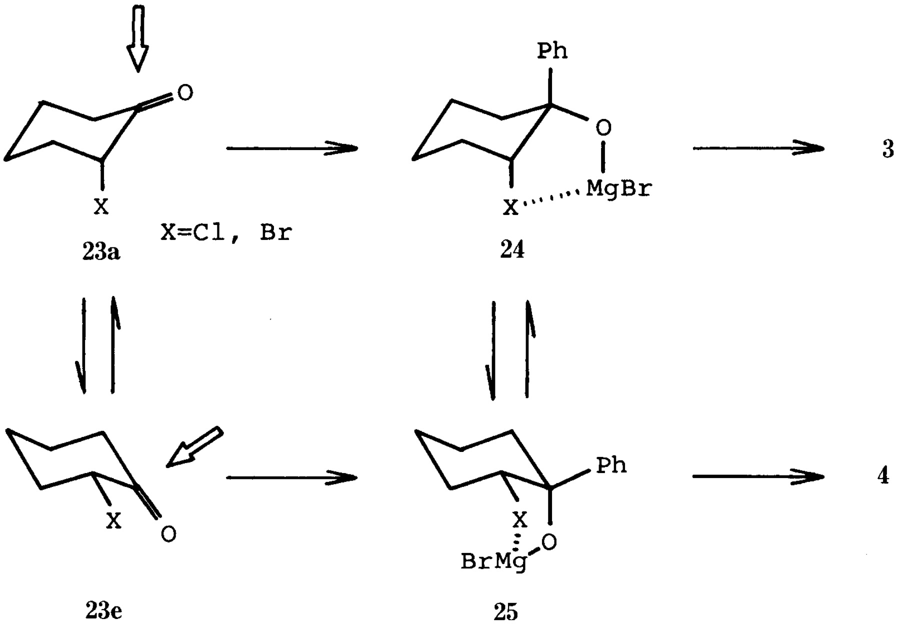


Chart 2

axial side to give a migrated product **3** by way of the intermediate **24**. Another possible intermediate **25** (X = Br) would not be as favorable as **24** even in THF because of the steric repulsion between the equatorial bromine atom and the synclinal phenyl and metalloxyl groups.

The chlorine atom occupies the axial position and the larger methyl group occupies the equatorial position[3)] in the methyl congener **12**. Compound **16** is the main product formed from the chloroketone **12**, presumably by way of **26**, together with a small amount of **17**. The formation of **17** can be explained in terms of isomerization of **12** or the intermediate **26** to another conformer (axial Me, equatorial Cl). In a similar way, the reaction of **12** with methylmagnesium iodide yielded **18** as the major product and **19** as shown in Table IV. Sisti and Vitale[4)] reported that **12** gave **19** as the major product (40%) and **18** (26%) on treatment with methyllithium and isopropylmagnesium bromide in benzene successively. However, they did not propose a mechanism for the preferential production of **19** over **18**. In their experiments, the chlorohydrin obtained from **12** and methyllithium was isolated and then treated with isopropylmagnesium bromide in benzene. We assume that the chlorohydrin is interconverted between **27** and another conformer **28** more easily than its metal salt, and that **28** is slightly preferable to **27** because of the difference of the 1,3-diaxial interactions in **27** and **28**. The magnesium salt of **28** is difficult to isomerize to the salt of **27** in benzene and undergoes ring contraction to form **19**.

Ring contraction of **10** to a four-membered ring is energetically unfavorable. The conformations of the seven-membered ring compound **13** and the eight-membered ring compound **14** are "flexible." In these three cases, the arrangement between the migrating methylene or phenyl group and the leaving chlorine atom deviated from antiperiplanarity in the halohydrin salts. Consequently, the rearranged products were obtained only in poor yields.

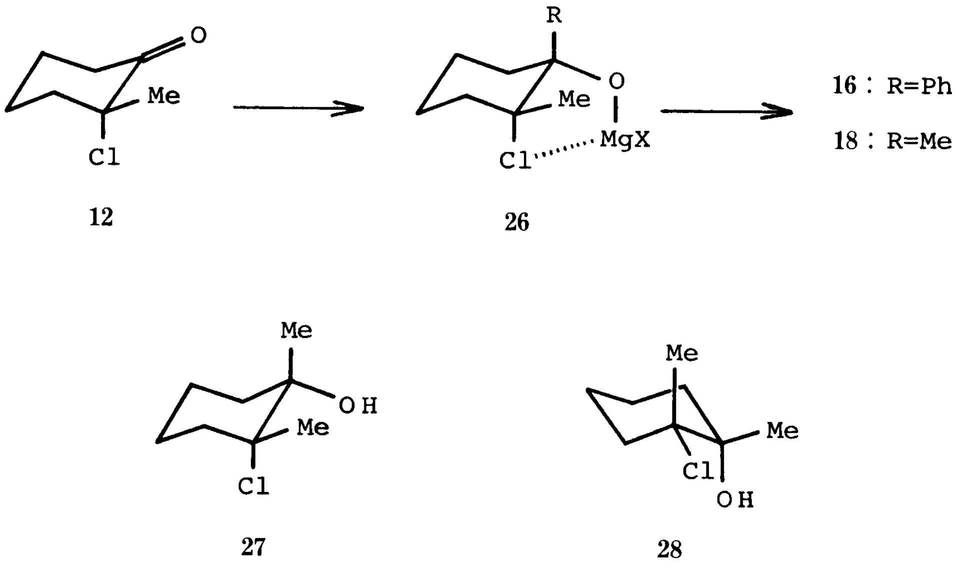


Chart 3

Experimental

Boiling points and melting points are uncorrected. Infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra and mass spectra (MS) were taken on a JASCO IRA-1 spectrometer, a Hitachi R-20B nuclear magnetic resonance instrument (with tetramethylsilane as an internal standard) and a JEOL JMS-D300 spectrometer, respectively. Thin-layer chromatography was performed with a Chromatotron, model 7924 (Harrison Research), on silica gel (Merck Kieselgel 60PF254 gypsum, Art. 7749). Column chromatography was performed on silica gel (Fuji-

Davison Silica gel BW-820MH).

Materials——2-Chlorocyclohexanone (**1**)[1c] was prepared by the reaction of cyclohexanone with sulfuryl chloride in CCl_4 and was purified by fractional distillation, bp 90—91 °C (14 mmHg). 2-Chlorocyclopentanone (**10**),[5] 2-chlorocycloheptanone (**13**)[5] and 2-chlorocyclooctanone (**14**)[6] were prepared by the reactions of the corresponding cyclanones with *N*-chlorosuccinimide in the presence of a catalytic amount of azoisobutyronitrile in CCl_4, **10**: bp 83—85 °C (13 mmHg), **13**: bp 98—100 °C (15 mmHg), **14**: bp 110—112 °C (14 mmHg). 2-Bromocyclohexanone (**11**) was prepared by the method of Schmid and Karrer,[7a] bp 104—106 °C (14 mmHg). 2-Chloro-2-methylcyclohexanone (**12**) was prepared by the method of Warnhoff *et al.*[8] Diphenylmagnesium was prepared by the method of Schlenk and Schlenk.[9]

Reaction of 2-Chlorocyclohexanone and Phenylmagnesium Bromide——a) Procedure A: The reaction was carried out by the method of Newman and Farbman.[1c] From the reaction mixture of 0.050 mol of **1** with 0.060 mol of phenylmagnesium bromide, the distillate was obtained and chromatographed (hexane–CH_2Cl_2 (2 : 1)) to give 4.79 g (55%) of **3**. bp 120—123 °C (3 mmHg), mp 54—57 °C (hexane) [lit.[1c] bp 136—137 °C (5—6 mmHg), mp 53—55 °C]. IR (KBr): 1705 cm^{-1} (C=O). The 2,4-dinitrophenylhydrazone (2,4-DNP) of **3** melted at 137—139 °C (methanol) [lit.[1e] mp 138—139 °C]. A small amount of **4** was eluted before **3** in column chromatography.

b) Procedure B: A solution of 6.63 g (0.050 mol) of **1** in 10 ml of dry ether was added dropwise to a solution of phenylmagnesium bromide (0.060 mol; from 9.42 g of bromobenzene and 1.46 g of magnesium in 60 ml of dry ether) with stirring at room temperature. Stirring was continued for 2 h and then the ether was replaced by 50 ml of THF. After refluxing for 12 h, the reaction mixture was cooled and poured into cold saturated NH_4Cl solution. After evaporation of THF, the mixture was extracted with benzene–ether (1 : 1). Then the extract was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed and then residue was vacuum-distilled through a Vigreux column. The fraction that boiled at 115—120 °C (3 mmHg) was collected (4.36 g). A part of the fraction (1.00 g) was thin-layer-chromatographed with a Chromatotron using hexane–CH_2Cl_2 (5 : 1) as the eluent to give 0.88 g (44%) of **4** and 0.10 g (5%) of **3**. **4**: IR (CCl_4): 1675 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 3.40—3.92 (1H, m, CHC=O), 7.25—7.55 (3H, m, ArH), 7.80—8.15 (2H, m, ArH). MS *m/z*: 174 (M$^+$). 2,4-DNP: mp 141—143 °C [lit.[10] mp 142—143 °C].

In Tables III and IV, the reactions with benzene as a solvent correspond to procedure A and those with THF to procedure B, and they gave the following products.

2-(*p*-Tolyl)cyclohexanone (**5**): bp 137—139 °C (2 mmHg), mp 47—51 °C [lit.[1e] bp 121—125 °C (0.7 mmHg), mp 49—50 °C]. IR (film): 1705 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 2.30 (3H, s, CH_3). 2,4-DNP: mp 156—158 °C [lit.[1e] mp 156—157 °C].

Cyclopentyl *p*-Tolyl Ketone (**6**): IR (film): 1680 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 2.41 (3H, s, CH_3Ar), 7.24 (2H, br d, J=9 Hz, ArH), 7.92 (2H, br d, J=9 Hz, ArH). MS *m/z*: 188 (M$^+$). 2,4-DNP: mp 119—121 °C [lit.[11] mp 119—120 °C].

2-(*p*-Chlorophenyl)cyclohexanone (**7**): bp 142—148 °C (1 mmHg), mp 75—77 °C [lit.[12a] bp 110—120 °C (0.1 mmHg), mp 77—78 °C]. IR (KBr): 1710 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 7.36 (4H, s, ArH). 2,4-DNP: mp 162—164 °C [lit.[12b] mp 163—164 °C].

p-Chlorophenyl Cyclopentyl Ketone (**8**): bp 136—143 °C (3 mmHg) [lit.[13] bp 95 °C (0.1 mmHg)]. IR (film): 1680 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 3.42—3.97 (1H, m, CHC=O), 7.32 (4H, br s, ArH). MS *m/z*: 208 (M$^+$). 2,4-DNP: mp 99—101 °C [lit.[13] mp 100—101 °C].

2-(*p*-Methoxyphenyl)cyclohexanone (**9**)[1f]: bp 173—177 °C (2 mmHg). IR (KBr): 1725 cm^{-1} (C=O). 2,4-DNP: mp 144—145 °C [lit.[1f] mp 144—145 °C].

2-Phenylcyclopentanone (**15**): bp 120—123 °C (2 mmHg) [lit.[14] bp 115—117 °C (1 mmHg)]. IR (film): 1740 cm^{-1} (C=O). 2,4-DNP: mp 143—144 °C [lit.[14] mp 142—144 °C].

2-Methyl-2-phenylcyclohexanone (**16**): bp 103—107 °C (4 mmHg) [lit.[1c] bp 95.5—96.5 °C (1 mmHg)]. IR (film): 1715 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 1.21 (3H, s, CH_3). 2,4-DNP: mp 174—175 °C [lit.[15] mp 174 °C].

1-Methylcyclopentyl Phenyl Ketone (**17**): IR (film): 1680 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 1.39 (3H, s, CH_3), 7.20—7.55 (3H, m, ArH), 7.80—8.10 (2H, m, ArH). MS *m/z*: 188 (M$^+$). 2,4-DNP: mp 109—111 °C [lit.[15] mp 109 °C].

2,2-Dimethylcyclohexanone (**18**) and 1-Acetyl-1-methylcyclopentane (**19**): A mixture of **18** and **19**, bp 50—55 °C (18 mmHg), which were characterized by ^{1}H-NMR. **18**: ^{1}H-NMR (CCl_4) δ: 1.02 (6H, s, $CH_3 \times 2$). **19**: ^{1}H-NMR (CCl_4) δ: 1.11 (3H, s, CH_3), 2.03 (3H, s, CH_3C=O).

2-Phenylcycloheptanone (**20**): bp 134—137 °C (4 mmHg) [lit.[16a] bp 136—138 °C (4 mmHg)]. IR (film): 1700 cm^{-1} (C=O). 2,4-DNP: mp 171—173 °C [lit.[16b] mp 171—172 °C].

Cyclohexyl Phenyl Ketone (**21**): mp 52—56 °C [lit.[10] 55—75 °C]. IR (KBr): 1690 cm^{-1} (C=O). ^{1}H-NMR (CCl_4) δ: 2.92—3.47 (1H, m, CHC=O), 7.10—7.61 (3H, m, ArH), 7.65—8.12 (2H, m, ArH). MS *m/z*: 188 (M$^+$). 2,4-DNP: mp 196—197 °C [lit.[10] mp 196—197.5 °C].

2-Phenylcyclooctanone (**22**): bp 130—135 °C (1 mmHg) [lit.[17] bp 133—135 °C (1.7 mmHg)]. IR (film): 1695 cm^{-1} (C=O). MS *m/z*: 202 (M$^+$). 2,4-DNP: mp 151—152 °C [lit.[17] mp 153 °C].

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