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Alkyl phosphines promoted reductive coupling of acyl cyanides: formation of *O*-acyl cyanohydrins

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Abstract—The reductive coupling of acyl cyanides promoted by alkyl phosphines has been discovered. Under mild reaction conditions, the substituted cyanohydrins were obtained in moderate to high yields by using trimethylphosphine or tributylphosphine as a promoter. The possible mechanism involved in the reaction was discussed on the basis of deuterium labeling and control experiments, indicating that one hydride transfer took place from alkyl phosphine to *O*-acyl cyanohydrin.

1. Introduction

Cyanohydrins are of synthetic interest as they can be transformed into a number of relevant functional groups such as β-amino alcohols, α-hydroxyacids and α-hydroxyesters, α-sulfonyloxynitriles, α-aminonitriles, α-fluoronitriles, 3-amino-2-alkenoates, and substituted azacycloalkenes.[1] The synthesis of cyanohydrins and their *O*-protected derivatives can be accomplished by enzymes,[2] organocatalysts,[3] and metal complexes.[4–7] Among various cyanide ion sources, trimethylsilyl cyanide,[8] methyl cyanoformate,[9] and acyl cyanides[10] are safer and commercially available reagents. With these cyanide ion sources, reactions between acyl cyanides and aldehydes are very efficient synthetic methods to give cyanohydrin derivatives in good yields.[11] While reductive coupling of acyl cyanides themselves was attained through Zn/HCl or hydrogenation in the presence of a Ni catalyst,[12] titanous chloride,[13] photoreduction,[14] and electrochemical reduction.[15] To the best of our knowledge, reductive coupling of acyl cyanides using organocatalysts has not been studied thoroughly.

More recently, organocatalysts, metal-free organic compounds, which exhibit catalytic abilities in organic reactions, have received much attention because of their advantages from an environmental as well as a resource standpoint.[16] Phosphines are widely used as Lewis bases or ligands in organic chemistry.[17] Some selected examples are their applications in the Baylis–Hillman reaction.[18] Another significant application of phosphines in organic reactions is the reduction of azides to amines in the Staudinger reaction.[19] Recently, we reported the reduction of activated carbonyl groups in α-keto esters, benzils, 1,2-cyclohexanedione, and α-ketophosphonates to the corresponding hydroxyl compounds by alkyl phosphines.[20] Herein, we report another application of alkyl phosphines in the reductive coupling of various acyl cyanides to produce *O*-acyl cyanohydrins in good yields under mild conditions, which is an effective novel reducing agent for converting carbonyl group into hydroxyl group containing compounds.

2. Results and discussion

Initially, we examine the phosphine Lewis base effects for the reduction of benzoyl cyanide. We found that the reaction of benzoyl cyanide **1a** with 1.0 equiv of trimethylphosphine (PMe_3) in THF (a THF solution) at room temperature for 6 h afforded the corresponding cyanohydrin **2a**, a reductive coupling product, in 80% yield (Table 1, entry 1). The results are summarized in Table 1. Additionally, when tributylphosphine (PBu_3) was used as a promoter, the isolated yield of **2a** was 51% under identical conditions (Table 1, entry 2). In the case of using diphenylmethylphosphine (PPh_2Me) or dimethylphenylphosphine ($PPhMe_2$) as a promoter, complicated products were obtained on the basis of TLC analysis (Table 1, entries 3 and 4). Triphenylphosphine (PPh_3), tricyclohexylphosphine (PCy_3), ethyl phosphite [$P(OEt)_3$], and various amines such as DBU, DMAP, DABCO, and pyridine have no activities in the reductive coupling of benzoyl cyanide (Table 1, entries 5–11).

Keywords: Acyl cyanide; Alkyl phosphine; Cyanohydrins; Hydride transfer; Deuterium labeling experiment.
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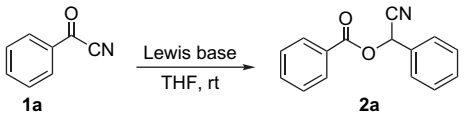
Table 1. Reductive coupling of benzoyl cyanide using various Lewis base promoters[a]



1a **2a**

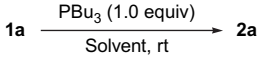
Entry	Lewis base	Time/h	**2a**[b]/%
1	PMe_3	6	80
2	P^nBu_3	6	51
3	PPh_2Me	12	—[c]
4	$PPhMe_2$	12	—[c]
5	PPh_3	24	NR[d]
6	PCy_3	24	NR[d]
7	$P(OEt)_3$	24	NR[d]
8	DBU	24	NR[d]
9	DMAP	24	NR[d]
10	DABCO	24	NR[d]
11	Pyridine	24	NR[d]

[a] All reactions were carried out using benzoyl cyanide **1a** (0.5 mmol) and Lewis base (0.5 mmol) in THF (0.5 mL, 1.0 M) at room temperature under argon atmosphere.
[b] Isolated yields.
[c] Complicated reactions took place.
[d] No reaction took place. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP: 4-dimethylaminopyridine, DABCO: 1,4-diazabicyclo[2.2.2]-octane, THF: tetrahydrofuran.

Next, to examine the solvent effect of this reductive coupling reaction, we carried out the reaction of **1a** with PBu_3 in various solvents (Table 2). Using toluene or dichloromethane as solvent, **2a** was obtained in 78 and 72% yields, respectively (Table 2, entries 2 and 4). On the other hand, using THF or MeCN as solvent, the achieved yields were slightly lower (Table 2, entries 1 and 3). In MeOH, no reaction occurred (Table 2, entry 5). Therefore, the optimized condition is using PMe_3 as a reductive coupling reagent in THF at room temperature for 6 h.

A variety of acyl cyanides were tested under these optimized conditions (Table 3). For a variety of aromatic acyl cyanides, the corresponding reductive coupling products **2** were obtained in good yields. Using sterically encumbered acyl cyanide **1d** as a substrate, the corresponding reductive coupling product **2d** was obtained in slightly lower yield (52%) compared with the *para*- or *meta*-chloro substituted substrates **1b** and **1c** (Table 3, entries 2–4). With respect to the electron-neutral and electron-rich acyl cyanides, the reactions proceeded smoothly to provide the corresponding cyanohydrin products **2** in good to high yields (Table 3, entries 5–7). The reductive coupling reaction of furan-2-carbonyl cyanide **1h** also proceeded smoothly under the standard conditions to give the corresponding product **2h** in 74% yield (Table 3, entry 8).

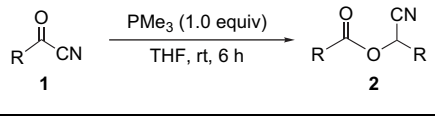
Table 2. Reductive coupling of benzoyl cyanide using tributylphosphine in various solvents[a]



Entry	Solvent	Time/h	**2a**[b]/%
1	THF	6	51
2	PhMe	6	78
3	MeCN	6	50
4	CH_2Cl_2	6	72
5	MeOH	24	NR[c]

[a] All reactions were carried out using benzoyl cyanide **1a** (0.5 mmol) and PBu_3 (0.5 mmol) in solvent (0.5 mL, 1.0 M) at room temperature under argon.
[b] Isolated yields.
[c] No reaction took place.

Table 3. Reductive coupling of acyl cyanides in the presence of trimethylphosphine[a]

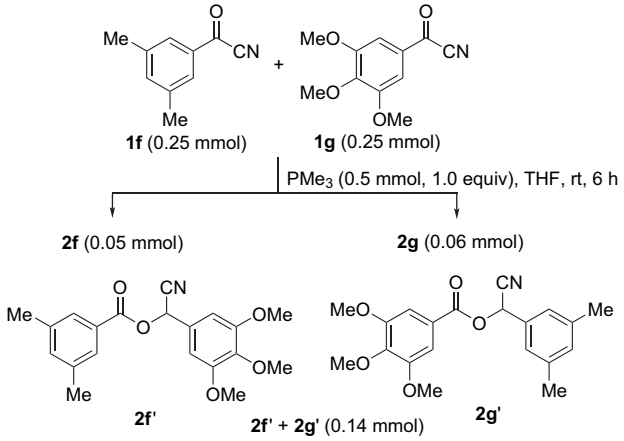


1 **2**

Entry	R	**2**, %[b]
1	C_6H_5 (**1a**)	**2a**, 80
2	4-ClC_6H_4 (**1b**)	**2b**, 89
3	3-ClC_6H_4 (**1c**)	**2c**, 78
4	2-ClC_6H_4 (**1d**)	**2d**, 52
5	4-MeC_6H_4 (**1e**)	**2e**, 78
6	3,5-$Me_2C_6H_3$ (**1f**)	**2f**, 91
7	3,4,5-$(MeO)_3C_6H_2$ (**1g**)	**2g**, 74
8	2-Furan (**1h**)	**2h**, 74

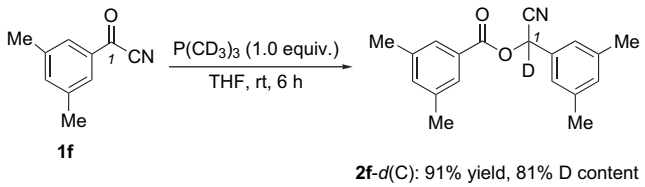
[a] All reactions were carried out using acyl cyanides (0.5 mmol) and PMe_3 (0.5 mL, 0.5 mmol, 1.0 M in THF) at room temperature under argon atmosphere for 6 h.
[b] Isolated yields.

The reaction mechanism is the most interesting issue in this context. In order to clarify the reaction mechanism, an intercrossing experiment between substrates **1f** and **1g** was carried out in the presence of PMe_3 under identical conditions (Scheme 1). As can be seen from Scheme 1, four reductive coupling products were formed in this reaction as isolated products **2f** (0.05 mmol) and **2g** (0.06 mmol) as well as a mixture of **2f′/2g′** (0.14 mmol). This result indicated that the coupling reaction proceeded through an intermolecular reductive condensation of **1**.



Scheme 1. Intercrossing experiment between **1f** and **1g** in the presence of trimethylphosphine.

In order to identify the hydride source in these reductive coupling reactions, the reductive coupling of **1f** with trimethylphosphine-d_9, prepared from the reaction of CD_3MgI with tri-*o*-tolyl phosphite,[21] was carried out under the standard conditions and the product of **2f**-*d*(C) was produced in 91% isolated yield with 81% D incorporation at the C_1 position (Scheme 2).[22]

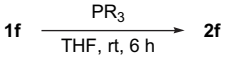


Scheme 2. Isotopic labeling experiment.

The deuterium labeling experiment indicated that only one D was transferred from phosphine to the product. This result suggests that only 0.5 equiv of PMe_3 is necessary in this reaction. Thus, we carried out this reaction using 0.5 equiv of PMe_3 under the standard conditions. As a result, the yield of **2f** decreased to 47%, indicating that 1.0 equiv of phosphine is essential in the reaction (Table 4, entry 1). Next, this reaction was carried out using 0.5 equiv of PMe_3 and 0.5 equiv of PPh_3 under otherwise identical conditions. We found that the yield of **2f** decreased to 41% (Table 4, entry 2). While using 0.5 equiv of PMe_3 and 0.5 equiv of $P(OBu)_3$ or PBu_3 or non-nucleophilic $^iPr_2NEt$, **2f** was obtained in 75, 85, and 65% yields, respectively (Table 4, entries 3–5). These results suggested that 50 mol % of phosphine such as PMe_3 or PBu_3 acted as a reductant and other 50 mol % of phosphine such as PMe_3, PBu_3 and $P(OBu)_3$ (phosphite), or $^iPr_2NEt$ acted as a promoter to quench the generated CN^- in the reaction process since $P(OBu)_3$ itself and amine cannot promote this reaction. Triphenylphosphine did not indicate the promoter effect in combination with trimethylphosphine presumably due to its steric bulkiness (Table 4, entry 2). In addition, by adding 30 mol % of 2,6-di(*tert*-butyl)-4-methylphenol (BHT) as a radical inhibitor in this reaction, the yield of **2f** was unaffected (87%), rendering unlikely the intervention of a radical pathway (Table 4, entry 6 and Table 3, entry 6).

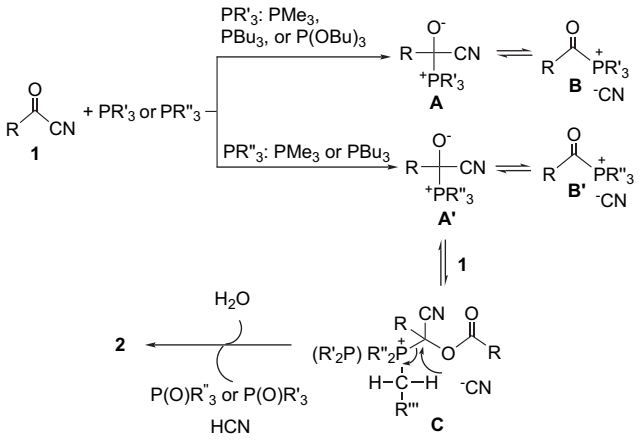
According to the relative control experiments, a plausible mechanism for the reductive coupling of acyl cyanides is proposed in Scheme 3. Initially, acyl cyanide **1** is probably activated by phosphine or phosphite to form intermediates **A** or **A′**, which is in equilibrium with the corresponding intermediate **B** or **B′**.[23] Then the nucleophilic attack of **1** by intermediate **A** or **A′** in the following step to give intermediate **C**. The subsequent one hydride transfer from trimethylphosphine or tributylphosphine to the carbon connected to

Table 4. Reduction of benzyl cyanide **1f** in the presence of various phosphines, phosphite, and amine[a]



Entry	PR_3	**2f**[b]/%
1	PMe_3 (0.5 equiv)	47
2	PMe_3 (0.5 equiv), PPh_3 (0.5 equiv)	41
3	PMe_3 (0.5 equiv), $P(OBu)_3$ (0.5 equiv)	75
4	PMe_3 (0.5 equiv), PBu_3 (0.5 equiv)	85
5	PMe_3 (0.5 equiv), $^iPr_2NEt$ (0.5 equiv)	65
6[c]	PMe_3 (1.0 equiv)	87

[a] All reactions were carried out using benzoyl cyanide **1f** (0.5 mmol) and PR_3 (0.5 mmol) in THF (0.5 mL, 1.0 M) at room temperature under argon atmosphere.
[b] Isolated yields.
[c] 2,6-Di(*tert*-butyl)-4-methylphenol (0.15 mmol) was added in the reaction.



Scheme 3. A proposed reaction mechanism.

CN group takes place to give product **2** and the corresponding phosphine oxide[24] and HCN by ambient moisture or during work-up (Supplementary data).[20] This H transfer only takes place when R′ or R″ is an alkyl group that is the driving force to move these equilibriums forward to form the final product. When PR'_3 is $P(OBu)_3$ in intermediate **C**, the reaction will not take place to produce the final product and will go back to the reversed way to intermediates **A** and **A′** or **B** and **B′** to generate the reactive intermediate. In addition, the generated HCN is quenched by other 0.5 equiv of phosphine or phosphite during the reaction. This is why using 50 mol % of PMe_3 and 50 mol % of $P(OBu)_3$, **2f** can be still obtained in good yield. The more detailed mechanistic investigation is undergoing to figure out the key factor of this interesting reductive coupling reaction promoted by alkyl phosphine.

3. Conclusion

In summary, we disclosed an efficient reductive coupling reaction of acyl cyanides to form *O*-acyl cyanohydrin products. These reactions could take place at room temperature in the presence of alkyl phosphines such as trimethylphosphine in THF or tributylphosphine in various solvents within 6 h to give the corresponding products in good yields. We confirmed that this was an intermolecular reductive coupling reaction of acyl cyanide by a hydride transfer from alkyl phosphine to the carbonyl group. Efforts are underway to elucidate the mechanistic details of this reductive system and to extend the scope of substrates in this reductive coupling reaction.

4. Experimental

4.1. General

Melting points were obtained with a Yanagimoto micro melting point apparatus and were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded for a solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. *J*-values are in hertz. Mass spectra were recorded with an HP-5989 instrument and HRMS was measured by a Finnigan MA^+ mass spectrometer. The solid compounds reported in this paper gave satisfactory CHN microanalyses with

a Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. Reaction experiments were performed under argon condition. The starting materials **1b**–**1h**[25] were synthesized according to the previous literature.

4.2. Typical reaction procedure for the preparation of 2

A mixture of acyl cyanide (0.5 mmol) and PMe_3 (0.5 mL, 0.5 mmol, 1.0 M in THF) was stirred under argon at room temperature for the required time indicated in tables. After the reaction solution was concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum=1/20) to afford pure product **2**.

4.2.1. Benzoic acid cyano-phenyl-methyl ester (2a) (a known compound).[26] An off-white solid: 47 mg, 80% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 6.68 (s, 1H, CH), 7.45–7.50 (m, 6H, Ar), 7.60–7.65 (m, 2H, Ar), 8.06–8.09 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 63.3, 116.2, 127.8, 128.0, 128.6, 129.2, 130.0, 130.4, 131.8, 134.1, 164.6. MS (EI) *m/z*: 237 (M^+, 3.73), 116 (28.30), 105 (100), 77 (25.62).

4.2.2. 4-Chlorobenzoic acid (4-chlorophenyl)-cyano-methyl ester (2b) (a known compound).[15] A light yellow solid: 68 mg, 89% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 6.63 (s, 1H, CH), 7.44–7.48 (m, 4H, Ar), 7.55 (d, J=8.1 Hz, 2H, Ar), 7.98 (d, J=8.4 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.8, 115.6, 126.2, 129.0, 129.3, 129.5, 130.1, 131.3, 136.7, 140.8, 163.6.

4.2.3. 3-Chlorobenzoic acid (3-chlorophenyl)-cyano-methyl ester (2c). A light yellow oil: 60 mg, 78% yield. IR (CH_2Cl_2) ν 1738, 1428, 1243, 1196, 1120, 1069 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 6.63 (s, 1H, CH), 7.41–7.51 (m, 4H, Ar), 7.59–7.63 (m, 2H, Ar), 7.94–7.98 (m, 1H, Ar), 8.02–8.04 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.9, 115.4, 126.0, 128.0, 128.2, 129.4, 130.0, 130.1, 130.7, 130.8, 133.2, 134.3, 134.9, 135.3, 163.3. MS (EI) *m/z*: 306 (M^+, 2.26), 150 (22.58), 139 (100), 111 (22.35), 75 (23.83). HRMS (EI) for $C_{15}H_9NO_2Cl_2$: 305.0010; found: 305.0016.

4.2.4. 2-Chlorobenzoic acid (2-chlorophenyl)-cyano-methyl ester (2d) (a known compound).[15] A white solid: 40 mg, 52% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 6.96 (s, 1H, CH), 7.33–7.51 (m, 6H, Ar), 7.81–7.84 (m, 1H, Ar), 7.91 (d, J=7.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 61.1, 115.1, 126.8, 127.4, 127.7, 129.2, 129.7, 130.3, 131.5, 131.8, 132.0, 133.6, 133.8, 134.7, 163.1.

4.2.5. 4-Methylbenzoic acid cyano(4-methylphenyl)-methyl ester (2e) (a known compound).[15] A white solid: 52 mg, 78% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.40 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.62 (s, 1H, CH), 7.26 (t, J=6.6 Hz, 4H, Ar), 7.50 (d, J=8.1 Hz, 2H, Ar), 7.94 (d, J=8.1 Hz, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2, 21.7, 63.0, 116.4, 125.3, 127.8, 129.0, 129.3, 129.8, 130.0, 140.5, 144.9, 164.6. MS (EI) *m/z*: 265 (M^+, 8.14), 130 (42.40), 119 (100), 91 (29.56), 65 (32.29).

4.2.6. 3,5-Dimethylbenzoic acid cyano(3,5-dimethyl-phenyl)methyl ester (2f). A light yellow oil: 67 mg, 91% yield. IR (CH_2Cl_2) ν 3010, 2922, 2859, 1727, 1609, 1462, 1301 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.35 (s, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 6.60 (s, 1H, CH), 7.10 (s, 1H, Ar), 7.21 (s, 2H, Ar), 7.24 (s, 1H, Ar), 7.67 (s, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.0, 21.1, 63.2, 116.4, 125.6, 127.6, 127.9, 131.7, 131.9, 135.6, 138.2, 138.9, 164.8. MS (EI) *m/z*: 293 (M^+, 4.18), 144 (16.48), 133 (100), 105 (11.43). HRMS (MALDI) for $C_{19}H_{19}NO_2Na^+$: 316.1315; found: 316.1308.

4.2.7. 3,4,5-Trimethoxybenzoic acid cyano(3,4,5-trimethoxyphenyl)methyl ester (2g). A yellow solid: 77 mg, 74% yield. Mp: 137–139 °C. IR (CH_2Cl_2) ν 2941, 1727, 1593, 1464, 1338, 1211 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 3.88 (s, 3H, OCH_3), 3.91 (s, 6H, $2OCH_3$), 3.92 (s, 6H, $2OCH_3$), 3.93 (s, 3H, OCH_3), 6.63 (s, 1H, CH), 6.82 (s, 2H, Ar), 7.31 (s, 2H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 56.1, 56.2, 60.7, 60.8, 63.5, 105.0, 107.2, 116.1, 122.7, 127.0, 139.4, 143.1, 152.9, 153.6, 164.2. MS (EI) *m/z*: 418 (M^++1, 18.88), 205 (100), 194 (88.24), 93 (1.41), 81 (4.68). Anal. Calcd for $C_{21}H_{23}NO_8$: C, 60.43%; H, 5.55%; N, 3.36%; found: C, 60.40%; H, 5.64%; N, 3.13%.

4.2.8. Cyano(furan-2-yl)methyl furan-2-carboxylate (2h). A yellow solid: 40 mg, 74% yield. Mp: 122–124 °C. IR (CH_2Cl_2) ν 2923, 1732, 1470, 1394, 1280, 1099 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 6.46–6.48 (m, 1H, Fu), 6.55–6.57 (m, 1H, Fu), 6.72 (s, 1H, CH), 6.76–6.78 (m, 1H, Fu), 7.32–7.33 (m, 1H, Fu), 7.53–7.55 (m, 1H, Fu), 7.64–7.66 (m, 1H, Fu). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.8, 111.1, 112.3, 113.0, 116.9, 120.5, 142.3, 145.2, 146.3, 147.8, 156.1. MS (EI) *m/z*: 217 (M^+, 1.74), 106 (89.00), 95 (100), 77 (15.07), 51 (19.96). HRMS (EI) for $C_{11}H_7NO_4$: 217.0375; found: 217.0380.

Acknowledgements

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