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Direct Conversion of Secondary Phosphine Oxides and *H*-Phosphinates with [Di(acyloxy)iodo]benzenes to Phosphinic and Phosphonic Amides

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ABSTRACT: *The reaction of [di(acyloxy)iodo]-benzene with secondary phosphine oxides or H-phosphinates in the presence of primary or secondary amines allows one to obtain phosphinic or phosphonic acids amides in the one-pot process. We take advantage of the strong acylating system DAIB/$R_2P(O)H$ to phosphinylation of amines. However, the reaction mechanism is multipathway and causes yields of phosphinic or phosphonic acids amides to be moderate. When the concentration of amines is low, the intermolecular process plays a main role leading to the formation of carboxylic amides through mixed phosphoric–carboxylic anhydride, and also in the low concentration of amines, tetrahydrofuran effectively competes with the amines in the nucleophilic attack on the acylating intermediates.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:81–86, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20514

INTRODUCTION

Despite the fact that first hypervalent organoiodine compound was synthesized by Wilgerodt in 1886 [1], and hypervalent iodine reagents are widely used in organic transformations [2,3], reactivity of hypervalent organoiodine compound with organophosphorus reagents is still considerably unexplored area. There are only a few publications concerning reactions of usual hypervalent organoiodine regents as [di(acetoxy)iodo]benzene, [bis(trifluoroacetoxy)iodo]benzene, iodozobenzene, or dichloroiodobenzene with phosphorus nucleophiles. In 1978, Foss published work concerning oxidation of diphosphines and trialkyl phosphites with iodozobenzene [4]. Lopusinski carried out a set of experiments between phosphor organic reagents such as triphenylphosphine, trialkyl phosphites, triarylphosphites with iodozobenzene and iodoxybenzene in the presence of montmorylonite or in the absence of such a catalyst [5]. Garreg et al. tried to use [di(acetoxy)iodo]benzene as a mild reagent for oxidation of *H*-phosphonates to phosphates in oligonucleotide synthesis [6]. An interesting aspect of the reactivity of hypervalent iodine organic compounds with phosphorus nucleophiles is the direct arylation of phosphorus acid salts [7], trialkyl phosphites [8], or phosphines [9] using aryliodonium salts.

Phosphorus analogs of Koser reagent [hydroxy((phosphoryl)oxy)iodo]benzenes and their reactivity exemplify an interesting aspect of hypervalent iodine and phosphor organic chemistry, particularly α-phosphoryloxylation of ketones [10,11] and preparation of alkynyl dialkyl phophates [12].

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In our research, we focused on the subject of the reactivity of hypervalent iodine compounds with phosphorus nucleophiles, such as dialkyl phosphites, trialkyl phosphites, secondary phosphine oxides, and aryl *H*-phosphinates, as well as on the problem of reactivity of hypervalent iodine compounds with aforementioned phosphorus nucleophiles in the presence of additional nucleophiles, for example, alcohols [13,14].

As we previously reported, the system [di(acyloxy)iodo]benzene and $R_2P(O)H$ is a strong acylating agent, which is able to acylate various oxygen nucleophiles as alcohols or carboxylic acids [13,14]. Moreover, the system of the Koser reagent $Ph(OTs)OH/R_2P(O)H$ in the absence of other better nucleophiles is able to acylate even ethers like THF, which demonstrates the acylating power of this system [15].

So far, our research in exploring properties of hypervalent iodine/organophosphorus nucleophile as an acylating system considers only acylation of oxygen species as sufficiently resistant to oxidation by hypervalent iodine compounds to ensure a clean route of reaction. However, now we would like to present results of research in which we examined the acylating properties of the hypervalent iodine/organophosphorus nucleophile system toward acylation of aliphatic amines, an alternative for the Todd–Atherton reaction [16].

RESULTS AND DISCUSSION

At first, we performed an experiment with commercially available [di(acetoxy)iodo]benzene **2** and diphenylphosphine oxide **1** in the presence of isobutyl amine. To take into consideration the higher nucleophilicity of amines compared with the nucleophilicity of alcohols and ethers, we performed first experiments with only 3 equiv of amine in the tetrahydrofuran (THF) solution. We had expected that because of the high nucleophilicity of amine, we would obtain mainly *N*-isobutyl diphenylphosphinic acid amide **9**.

However after workup and separation of the reaction mixture, we did not obtain any traces of *N*-isobutyl diphenylphosphinic acid amide **9**; instead, we isolated diphenylphosphinic acid **5** with 50% yield and *O*-(diphenylphosphinoyl)-*O′*-acetyl-1,4-butanediol **8** with 12% yield as a product of THF ring opening. In further experiments, we used [di(benzoyloxy)iodo]benzene as a hypervalent iodine reagent to facilitate isolation of carboxylic amides.

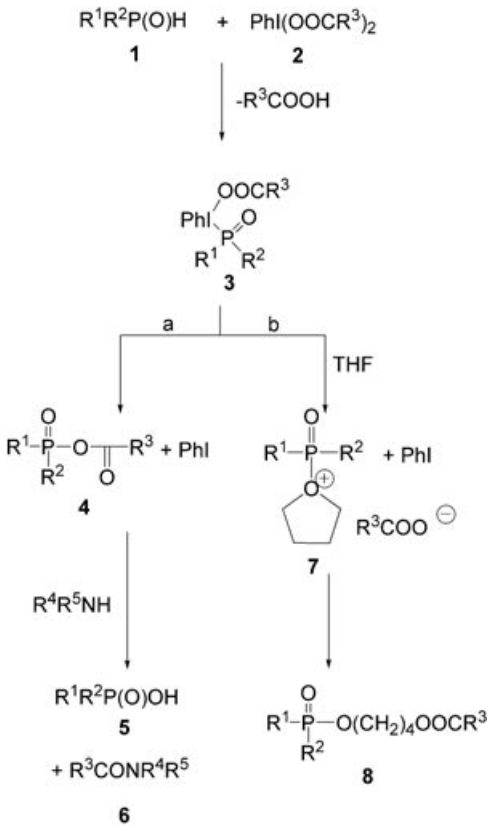
We performed a set of experiments with [di(benzoyloxy)iodo]benzene and diphenylphospine oxide or dibenzylphosphine oxide. The results of these experiments are presented in Table 1. From the reactions mixtures, we isolated THF ring opening products **8**, phosphinic acids **5**, and carboxylic amides **6**, and we did not isolate phosphinic acids amides **9**. On the basis of these experiments, and taking into consideration our previous works [14,15], we have proposed tentative mechanism of this reaction presented in Scheme 1.

At the first stage, the trivalent form of phosphorous nucleophiles reacts with the [di(acyloxy)iodo]benzene and forms intermediate **3**, which may undergo reactions in two ways. The first possibility pathway (a) is intermolecular collapse of **3** into phosphoric–carboxylic mixed anhydride, which undergoes further reaction with amine and produces as a final product carboxylic amide. Such a reaction of mixed anhydrides with amines is a well-known fast process [17], so we did not isolate mixed anhydride since it was immediately consumed in the reaction with amine. The second possibility pathway (b) is reaction of the intermediate **3** with THF, which is present in a large excess as a solvent leading to oxonium salt **7**, which undergoes reaction with carboxylic acid anion and produces *O*-(phosphinoyl)-*O′*-acyl-1,4-butanediol **8**.

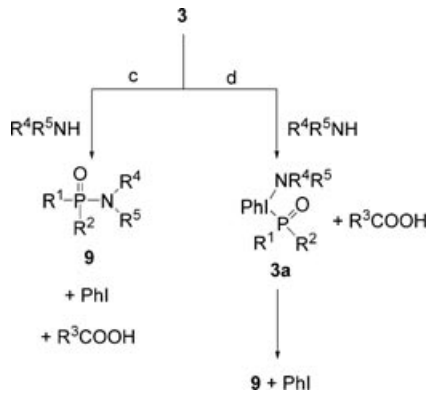
Surprisingly, we did not isolate any product of the nucleophilic attack of amine on the phosphorus atom in the intermediate **3**, meaning phosphinic acid amide, which we might expect, taking into consideration much higher nucleophilicity of amines compared with THF, but we had already noticed that

TABLE 1 Reaction of $R^1R^2P(O)H$ with [Di(benzoyloxy)iodo]benzene in the Presence of Amines R^4R^5NH in THF As a Solvent

				Yields (%)		
Run	R^1, R^2	R^4	R^5	**5**	**6**	**8**
1	Ph	H	*i*Bu	66	62	16
2	Bzl	H	*i*Bu	45	21	10
3	Bzl	Et	Et	50	60	20
4	Ph	Et	Et	77	29	14



SCHEME 1



SCHEME 2

the species type of **3** is an extremely reactive acylating agent, which we were able to observe only in ^{31}P NMR but were not able to isolate [14]. So, if this compound is extremely reactive, its selectivity is poor and probably it reacts quickly in solvent cage with any nucleophile whose concentration is higher. In typical experiment, the molar ratio of THF to amine is about 30:1, which explains why we could not isolate phosphinic acid amide.

Because we did not isolate phosphinic acid amides, we run experiments in amines as a solvent to make nucleophilic attack of amine on **3** possible and to exclude THF opening ring process. We performed experiments in which we treated the solution of $R^1R^2P(O)H$ phosphorus acids in appropriate amine with [di(benzoyloxy)iodo]benzene. From the reaction mixtures, we isolated phosphinic acid amides **9**, carboxylic amides **6**, and phosphinic acids **5**. The results are presented in Table 2.

Because of higher concentration of amines, we were able to push the reaction via pathway (c) Scheme 2 so as to produce phosphinic acid amide. However, intermolecular pathway (b) Scheme 1, which led to mixed phosphoric–carboxylic anhydride and in the further reaction with amine to carboxylic amide, was still present. It must be pointed that the formation of **9** may result by the pathway (c), besides the nucleophilic attack on the phosphorus atom in the intermediate **3**, we have to consider alternative pathway (d) with ligand exchange acyloxy group with amine with the formation of intermediate **3a** and subsequent intermolecular reaction leading to amide **9** and PhI. However, at this moment we do not have rational arguments to exclude or confirm one of them.

To confirm proposed mechanism and to exclude possibility that carboxylic amide is formed in the reaction [di(acyloxy)iodo]benzene) with amine, we run an independent experiment with [di(benzoyloxy)iodo]benzene) in the excess of isobutylamine as a solvent without **1** in which we did not observe the formation of any traces of **6**. Despite the cited reactions of mixed phosphorus–carboxylic anhydrides with amines [17], to additionally confirm

TABLE 2 Reaction of $R^1R^2P(O)H$ with [Di(benzoyloxy)iodo]benzene in the Presence of Amines As Solvents

				Yields (%)		
Run	R^1, R^2	R^4	R^5	**5**	**6**	**9**
5	Ph	Et	Et	34	29	34
6	Ph	H	*i*Bu	38	60	34
7	*n*-Hex	Et	Et	43	18	11

TABLE 3 Reaction of $R^1R^2P(O)H$ with [Di(acetoxy)iodo]benzene in the Presence of Amines As Solvents

					Yields (%)	
Run	R^1	R^2	R^4	R^5	**5**	**9**
8	Ph	Ph	H	*n*-Bu	33	34
9	Bzl	Bzl	H	*n*-Bu	54	30
10	Ph	*i*PrO	H	*n*-Bu	55	16
11	Ph	Ph	$(CH_2)_2O(CH_2)_2$		53	19
12	*n*-Hex	*n*-Hex	$(CH_2)_2O(CH_2)_2$		20	22
13	Ph	*i*PrO	H	*i*Bu	46	17

that in case of our model of anhydride only **6** is produced in the reaction of mixed phosphinic–carboxylic anhydride with amine, we performed an experiment, using diphenylphosphinic-benzoic anhydride obtained on the independent way (from diphenylphosphinic acid salt and acetyl chloride) with *N*,*N*-diethylamine, and in this reaction we observed formation of only carboxylic amide without any traces of phosphinic amide.

Taking into consideration that in performed experiments, phosphorus amides were produced in one-top process directly from secondary phosphine oxides or *H*-phosphinates. Similarly as in the Todd–Atherton reaction, we ran a set of experiments between commercially available [di(acetoxy)iodo]benzene and $R^1R^2P(O)H$ acids in the excess of amines to check the possibility of using the explored reaction for the quick preparation of phosphinic or phosphonic acids amides. The results are presented in Table 3. From the reactions mixtures, we have isolated phosphoric acids amides and also phosphinic or phosphonic acids, which confirm the competition of both processes by the pathways (a) and (c) and cause yields of phosphinic or phosphonic acids amides to be moderate.

EXPERIMENTAL

All reactions were carried out under argon atmosphere in dry solvents (THF was dried over potassium, chloroform over P_2O_5, alcohols over magnesium). Chromatography was carried out on Silica Gel 60 (0.15–0.3 mm) Macherey Nagel®. ^{31}P NMR and ^1H NMR spectra were recorded with a Varian apparatus at 200 or 500 MHz. [Di(acetoxy)iodo]benzene was purchased from Avocado (Karlsruhe, Germany).

[Di(benzoyloxy)iodo]benzene

[Di(benzoyloxy)iodo]benzene was obtained by the modification method described in literature [18]. A total of 10 mmol of [di(acetoxy)iodo]benzene and 20 mmol of benzoic acid was dissolved in 40 mL of $CHCl_3$ followed by five times repeated slow evaporation under reduced pressure. Residue was finally crystallized from $CHCl_3$/Hexane. Yield 70%, 3.12 g, mp = 155–157°C.

General Procedure for the Reactions of $R^1R^2P(O)H$ with [di(benzoyloxy)iodo]benzene in the Presence of Amines in THF As a Solvent [Runs 1–4]

To a solution of **1** (2 mmol) in THF (20 mL) and amine (8 mmol), [di(benzoyloxy)iodo]benzene (2 mmol, 0892 g) was added. Reaction mixture was stirred under argon at room temperature for 15 h. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (50 mL); Et_2O was washed off with 5% $NaHCO_3$ (3 × 5 mL) and 2 M HCl (2 × 5 mL), dried with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (chloroform–acetone, 15:1) to obtain **6** and **8**. Alkaline water layer was acidified with concentrated HCl and extracted with AcOEt (3 × 30 mL) and dried with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was crystallized from AcOEt–Hexane to obtain **5**.

Run 1: *O*-(Diphenylphosphinoyl)- *O′*-benzoyl-1,4-butanediol (126 mg, 16%).^1H NMR (200MHz, $CDCl_3$) δ: 1.9 (m, 4H), 4.05–4.15 (m, 2H), 4.3–4.4 (m, 2H), 7.35–7.6 (m, 9H), 7.75–7.9 (m, 4H), 8–8.08 (m, 2H); ^{31}P NMR (300MHz, $CDCl_3$) δ: 34.38; *N*-isobutyl benzamide (220 mg, 62%); Diphenylphosphinic acid (292 mg, 66%) mp = 189–191°C. ^{31}P NMR (300MHz, $CDCl_3$) δ: 34.18.

Run 2: *O*-(Dibenzylphosphinoyl)-*O′*-benzoyl-1,4-butanediol (80 mg, 10%).^1H NMR (200 MHz, $CDCl_3$) δ: 1.53–1.78 (m, 4H), 3.05 (t, J^{PH} = 15 Hz, 4H), 3.85 (t, 2H), 4.25 (t, 2H), 7.1–7.7 (m, 15H); ^{31}P NMR (300MHz, $CDCl_3$) δ = 51.26; *N*-isobutyl benzamide (70 mg, 21%); Dibenzylphosphinic acid (220 mg,

45%) mp = 187–189°C, ^{31}P NMR (300 MHz, $CDCl_3$) δ: 52.36.

Run 3: *O*-(Dibenzylphosphinoyl)-*O′*-benzoyl-1,4-butanediol (160 mg, 20%). ^{1}H NMR (200 MHz, $CDCl_3$); *N*,*N*-diethyl benzamide (212 mg, 60%); dibenzylphosphinic acid (246 mg, 50%).

Run 4: *O*-(diphenylphosphinoyl)-*O′*-benzoyl-1,4-butanediol (110 mg, 14%).; *N*,*N*-diethyl benzamide (102 mg, 29%); diphenylphosphinic acid (335 mg, 77%).

General Procedure for Reactions of $R^1R^2P(O)H$ with [Di(acyloxy)iodo]benzene in the Presence of Amines As Solvents

Runs 5–7. To a solution of **1** (2 mmol) in amine (100 mmol), [di(benzoyloxy)iodo]benzene (2 mmol, 0,892 g) was added. Reaction mixture was stirred under argon at room temperature for 15 h. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (50 mL); Et_2O was washed off with 5% $NaHCO_3$ (3 × 5 mL) and 2 M HCl (2 × 5 mL), dried with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (chloroform–acetone, 15:1) to obtain **6** and **9**. Alkaline water layer was acidified with concentrated HCl and extracted with AcOEt (3 × 30 mL) and dried with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was crystallized from AcOEt–Hexane to obtain **5.**

Run 5: *N*,*N*-Diethyl diphenylphosphinic acid amide (185 mg, 34%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.09 (t, 6H), 3.11 (m, 4H), 7.34–7.56 (m, 6H), 7.78–7.94 (m, 4H); *N*,*N*-diethyl benzamide (113 mg, 32%); diphenylphosphinic acid (148 mg, 34%).

Run 6: *N*-Isobutyl diphenylphosphinic acid amide (185 mg, 34%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.9 (d, 6H), 1.8 (m, 1H), 2.8 (t, J = 7.14 Hz, 2H), 3.1–3.45 (bs, 1H), 7.32–7.73 (m, 6H), 7.95–8.14 (m, 4H); ^{31}P NMR (300 MHz, $CDCl_3$) δ: 27.45; *N*-isobutyl benzamide (212 mg, 60%); diphenylphosphinic acid (165 mg, 38%).

Run 7: *N*,*N*-Diethyl di-*n*-hexylphosphinic acid amide (64 mg, 11%).^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.8–1.75 (m, 32H), 2.9–3.17 (m, 4H); ^{31}P NMR (300MHz, $CDCl_3$) δ = 50.72; *N*,*N*-diethyl benzamide (64 mg, 18%); di-*n*-hexylphosphinic acid (201 mg, 43%); ^{31}P NMR (300 MHz, $CDCl_3$) δ: 52.36.

Runs 8–13. To a solution of **1** (2 mmol) in amine (100 mmol), [di(acetoxy)iodo]benzene (2 mmol, 0.64 g) was added. Reaction mixture was stirred under argon at room temperature for 15 h. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (50 mL), Et_2O was washed off with 5% $NaHCO_3$ (3 × 5 mL) and 2 M HCl (2 × 5 mL), dried with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (chloroform–acetone, 15:1) to obtain **9**. Alkaline water layer was acidified with concentrated HCl and extracted with AcOEt (3 × 30 mL) and dried with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was crystallized from AcOEt–Hexane to obtain **5.**

Run 8: *N*-*n*-Butyl diphenylphosphinic acid amide (185 mg, 34%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.85 (t, 3H), 1.32 (m, 2H), 1.53 (m, 2H), 2.93 (m, 3H), 7.41 (m, 6H), 7.88 (m, 4H), ^{31}P NMR (300 MHz, $CDCl_3$) δ: 24.72; diphenylphosphinic acid (143 mg, 33%).

Run 9: *N*-*n*-Butyl dibenzylphosphinic acid amide (180 mg, 30%).^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.85 (t, 3H), 1.23 (m, 2H), 1.36 (m, 2H), 2.85 (q, 2H), 3.09 (m, 4H), 7.26 (m, 6H), 7.33 (m,4H), ^{31}P NMR (300 MHz, $CDCl_3$) δ = 38.42; dibenzylphosphinic acid (265 mg, 45%).

Run 10: *N*-*n*-Butyl *O*-isopropyl phenylphosphonic acid amide (82 mg, 16%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.85 (t, 3H), 1.26 (m, 2H), 1.29 (d, 3H), 1.36 (d, 3H), 1.42 (m, 2H), 2.84 (m, 3H), 4.74 (m, 1H), 7.44 (m, 3H), 7.80 (m, 2H), ^{31}P NMR (300 MHz, $CDCl_3$) δ = 22.56; isopropyl phenylphosphonate (224 mg, 56%).

Run 11: 4-Diphenylphosphinoyl-morpholine (109 mg, 19%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.07 (m, 4H), 3.70 (m, 4H), 7.47 (m, 6H), 7.87 (m, 4H), ^{31}P NMR (300 MHz, $CDCl_3$) δ: 30.25; diphenylphosphinic acid (239 mg, 55%).

Run 12: 4-(Di-*n*-hexylphosphinoyl)-morpholine (133 mg, 22%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.87 (t, 6H), 1.25–1.31 (m, 12H), 1.58–1.66 (m, 8H), 3.04 (m, 4H), 3.66 (m, 4H), ^{31}P NMR (300 MHz, $CDCl_3$) δ: 49.28; di-*n*-hexylphosphic acid (34 mg, 20%).

Run 13: *N*-Isobutyl *O*-isopropyl phenylphosphonic acid amide (85 mg, 17%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.85 (dd, 6H), 1.35 (dd, 6H), 1.62 (m, 1H), 1.36 (d, 3H), 2.65 (t, 2H), 2.96 (bs, 1H), 4.72 (m, 1H), 7.44 (m, 3H), 7.80 (m, 2H); isopropyl phenylphosphonate (184 mg, 46%).

REFERENCES

[1] Wilgerodt, C. J Prakt Chem 1886, 33, 154.
[2] Stang, P. J.; Zhdankin, V. V. Chem Rev 1996, 96, 1123.
[3] Varvoglis, A. Tetrahedron 1997, 53, 1197.
[4] Foss, W. L.; Wejch, J. A.; Lermontov, S. A.; Luchenko, I. F. Zh Obsch Khim 1977, 48, 1713.

[5] Mielniczak, G.; Łopusiński, A. Synlett 2001, 4, 505.
[6] Garegg, P. J.; Regberg, T.; Stawiński, J.; Stromberg, R. J Chem Soc Perkin Trans 1 1987, 1, 1271.
[7] Zu-Dong, L.; Zhen-Chu, C. Synthesis 1993, 4, 373.
[8] Varvoglis, A. G. Tetrahedron Lett 1972, 1, 31.
[9] Kitamura, T.; Furuki, R.; Nagata, K.; Taniguchi, H.; Stang, P. J. J Org Chem 1992, 57, 6810.
[10] Koser, G. F.; Lodaya, J. S.; Ray, D. G.; Kokil, P. B. J Am Chem Soc 1988, 110, 2987.
[11] Nabana, T.; Togo, H. J Org Chem 2002, 67, 4362.
[12] Stang, P. J.; Kitamura, T.; Boehshar, M.; Wingert, H. J Am Chem Soc 1989, 111, 2225.
[13] Makowiec, S.; Rachon, J. Phosphorus Sulfur Silicon 2002, 177, 941.
[14] Makowiec, S.; Rachon, J. Heteroat Chem 2003, 14(4), 352.
[15] Makowiec, S.; Rachon, J. Pol J Chem 2005, 79, 487.
[16] Atherton, F. R.; Todd, A. R. J Chem Soc 1947, 677.
[17] (a) Bentley, R. J Am Chem Soc 1948, 70, 2183; (b) Ramage, R.; Hopton, D.; Parrott, M. J.; Richardson, R. S.; Kenner, G. W.; Moore, G. A. J Chem Soc Perkin Trans 1 1985, 461; (c) Jaszay, Z. M.; Petnehazy, I.; Toeke, L. Synth Commun 1998, 28, 15, 2761.
[18] Merkushev, E. B.; Novikov, A. N.; Makarchenko, S. S.; Moskalchuk, A. S.; Glushkova, V. V.; Kogai, T. I.; Polyakova, L. G. Zh Org Khim 1975, 11, 1259.