A novel selective synthesis of β-isothiocyanato ketones

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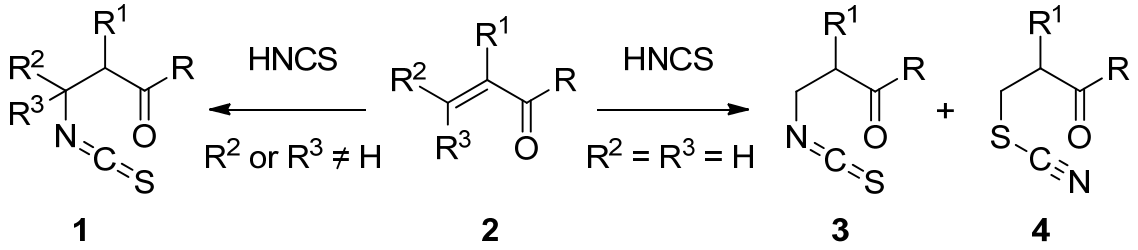
A new selective two-step synthesis of β-isothiocyanato ketones from α,β-unsaturated ketones has been developed. This synthesis includes preparation of β-azidoketones with subsequent reaction of these with triphenylphosphine and carbon disulfide. This approach is especially useful for synthesis of β-unsubstituted β-isothiocyanato ketones, which are impossible to prepare with sufficient purity via commonly used procedures.

Keywords: Azides; Isothiocyanates; Carbonyl Compounds; Phosphorus Compounds; Three-component Reaction

1. Introduction

β-Isothiocyanato aldehydes and ketones (e.g., **1**), possessing two reactive functional groups, have proved to be versatile starting materials for the synthesis of a wide range of nitrogen-containing acyclic and heterocyclic compounds. Since the first representatives of **1** have been described in 1946 [1], their chemistry was extensively studied [2, 3]. They were used in preparation of various pyrimidines [4–6], 1,3-thiazines [7, 8], 1,3-oxazines [9], pyridines [10], nucleosides [11,12], pyrroles [13], 1,2,4-triazepines [14], condensed heterocycles [15–17], etc.

The most commonly used synthesis of β-isothiocyanato aldehydes and ketones1involves the addition of thiocyanic acid to the corresponding α,β-unsaturated carbonyl compounds **2** (Scheme1) [1, 18, 19].



Scheme 1

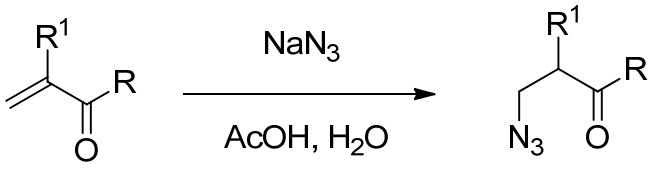
However, reaction of β-unsubstituted α,β-unsaturated aldehydes or ketones (**2**, $R^2 = R^3 = H$) with thiocyanic acid proceeds with low selectivity, resulting in mixtures of isomeric β-isothiocyanates **3** and β-thiocyanates **4** (up to 50 %) [20, 21], which are difficult to separate because of similar physical properties. This drawback confines the use of β-unsubstituted β-isothiocyanato aldehydes and ketones in organic synthesis.

We hypothesized that α,β-unsaturated aldehydes and ketones could be selectively transformed into respective β-isothiocyanato carbonyl compounds **1** and **3** by the addition of HN_3 to give β-azido aldehydes and ketones [22, 23] followed by transformation of the azido

group into an isothiocyanato group using a Staudinger/aza-Wittig sequence [24–30]. In our preliminary communication, an example of the application of this methodology has been described [31]. Herein, we report full details of the selective synthesis of β-unsubstituted β-isothiocyanato ketones from α,β-unsaturated ketones.

2. Results and discussion

Starting β-azido ketones **5a** and **5b** were prepared according to the literature procedure based on the reaction of methyl vinyl ketone (**6a**) and isopropenyl methyl ketone (**6b**) with sodium azide in aqueous acetic acid at room temperature (Scheme 2) [23].



6a-c **5a-c**

5-6 a R = Me, R^1 = H; **b** R = R^1 = Me; **c** R = Ph, R^1 = H

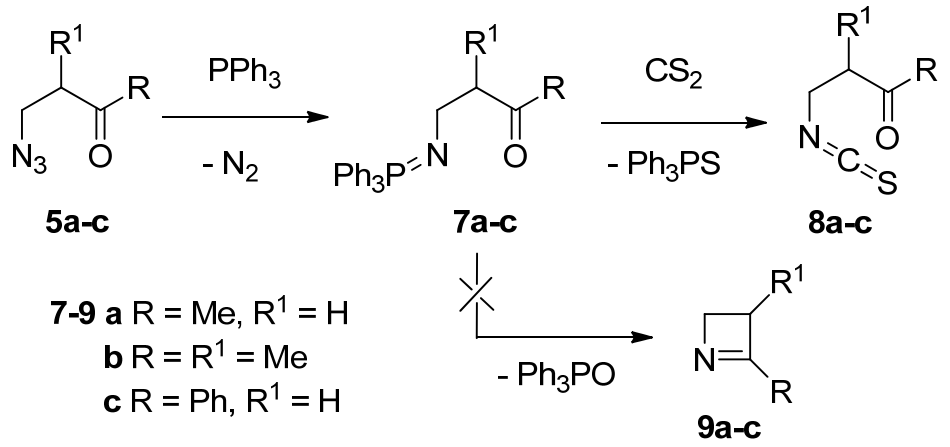
Scheme 2

β-Azido ketone **5c** was first synthesized following this procedure from phenyl vinyl ketone (**6c**). Previously, compound **5c** was obtained by reaction of 3-chloro-1-phenylpropan-2-one with sodium azide [32] or treatment of 1-phenylcyclopropanol with sodium azide in the presence of cerium (IV) ammonium nitrate [33].

Azides **5a–5c** were isolated from reaction mixtures as yellowish oils in 62–88 % yields after extraction with diethyl ether followed by neutralization of ether extracts with aqueous Na_2CO_3, drying and evaporation of solvent in vacuum. The purity of the crude **5a–5c** was excellent (>95 % according to ^{1}H NMR data), and they were used in further transformations without additional purification.

First, transformation of the azido group of compounds **5a–5c** into an isothiocyanato group was examined using azide **5a** as a starting material. After treatment of this compound with one equivalent of triphenylphosphine in anhydrous THF at room temperature, nitrogen evolution via

the Staudinger reaction was observed. Subsequent addition of excess of carbon disulfide to the obtained solution of iminophosphorane **7a** gave the target isothiocyanate **8a** (Scheme3). The latter was isolated after solvent removal and extraction of the residue with a petroleum ether–diethyl ether mixture (1:1). However, the yield of **8a** did not exceed 30 %.



Scheme 3

A more convenient procedure of synthesis of **8a** involved treatment of a solution of **5a** in THF-CS_2 with triphenylphosphine at room temperature for several hours. Yield of **8a** increased when after cessation of nitrogen evolution, the reaction mixture was refluxed for 1–1.5 h. Under optimal conditions (THF-CS_2, rt, 1.5 h, then reflux, 1 h), the yield of oily **8a** from azide **5a** was 53 % after vacuum distillation. Oily isothiocyanate **8b** and solid isothiocyanate **8c** were prepared analogously from azides **5b** and **5c** in 82 and 52 % yields, respectively. Notably, the products of intramolecular aza-Wittig reaction of iminophosphoranes **7a–7c**, azetines **9a–9c**, were not detected in the studied reactions. Previously, Eguchi et al. [34] reported the formation of 2-phenyl-1-azetine (**9c**) by the reaction of **5c** with PPh_3, however, in very low yield.

The reactions between azides **5a**, **5c** and triphenylphosphine (1 equiv.) with or without carbon disulfide in $CDCl_3$ were monitored by ^1H and ^{13}C NMR spectroscopy at 25 °C. According to the ^1H NMR spectroscopy data (Table 1, Fig. 1), the reaction of **5a** with PPh_3 in $CDCl_3$ was complete within 1.5 h to give iminophosphorane **7a** and methyl vinyl ketone (**6a**) in a 62:33 ratio, respectively. Ketone **6a** probably resulted from base-promoted elimination of hydrazoic acid from **5a** under the action of **7a**. Strong basic properties of iminophosphoranes are

well documented in the literature [24–29]. The formation of azetine **9a** was not detected in the NMR experiment.

Table 1. Reaction of **5a** with PPh_3 ($CDCl_3$, 25 °C)[a]: dependence of the products distribution on the reaction time

Time (min)	Products distribution (%)		
	5a	**7a**	**6a**
3	85	14	1
12	62	28	10
16	49	36	15
26	34	45	21
36	24	50	26
46	16	54	30
56	12	57	31
66	9	58	33
76	7	61	32
86	6	61	33
96	5	62	33

[a] A solution of PPh_3 (60.7 mg, 0.231 mmol) in 0.5 cm^3 $CDCl_3$ was added at once to a 5 mm NMR tube charged with **5a** (26.2 mg, 0.232 mmol). The solution obtained was shaken carefully (gas evolution!). The progress of the reaction was monitored by ^1H NMR spectroscopy (Bruker DPX-300).

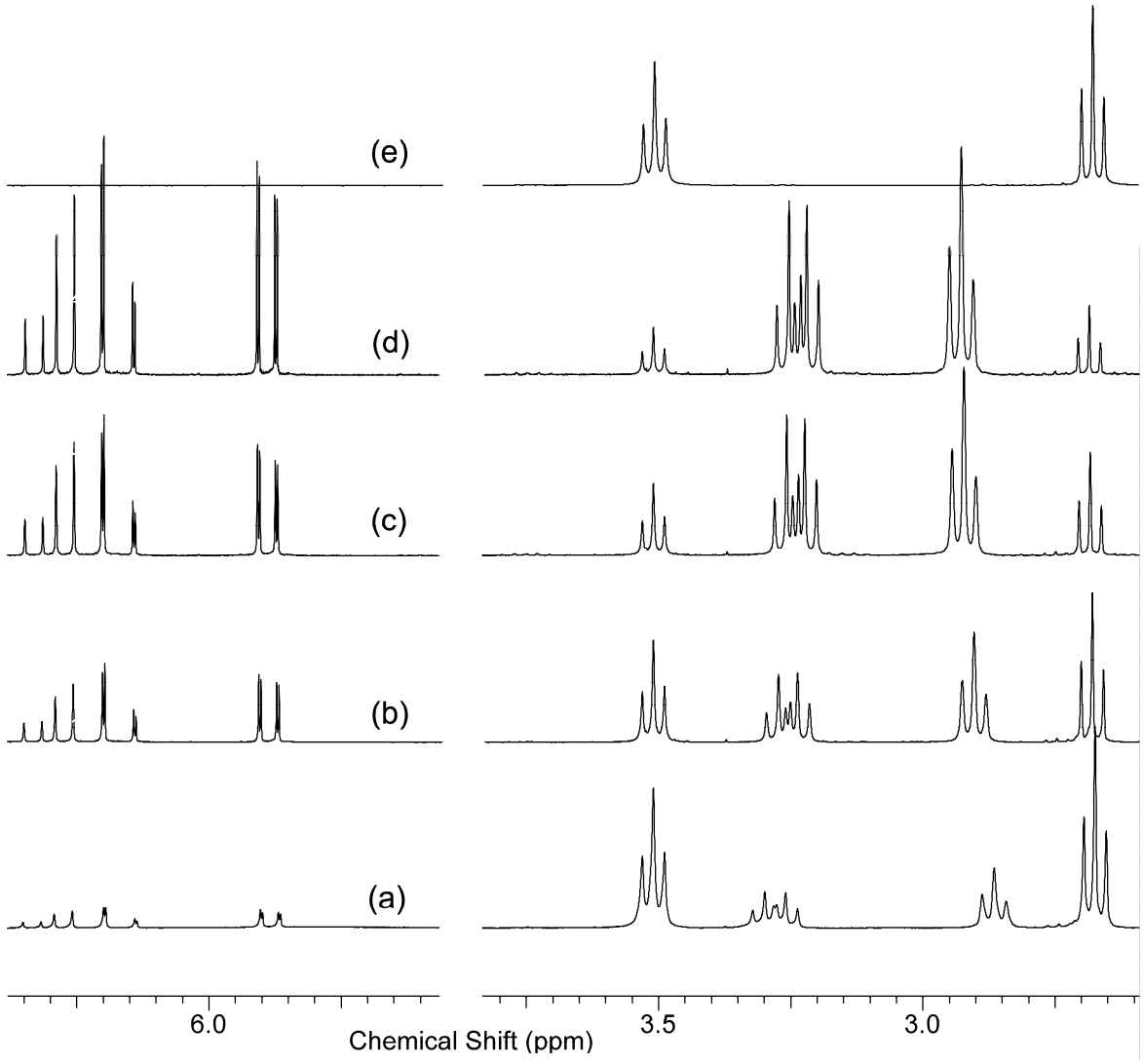


Fig. 1 a–d ^{1}H NMR spectra for the reaction of **5a** with PPh_3 ($CDCl_3$, 25 °C) after 12, 26, 46 and 66 min, respectively; **e** ^{1}H NMR spectra of **5a** in $CDCl_3$

The structure of iminophosphorane **7a** was confirmed by its ^{1}H and ^{13}C NMR spectra. Thus, the ^{1}H NMR spectrum of **7a** showed a singlet at 2.14 ppm because of the methyl group, a doublet of triplets at 3.24 ppm (^{3}J=6.7 and $^{3}J_{H,P}$=10.1 Hz) and a triplet at 2.97 ppm (^{3}J=6.7 Hz) assigned to the methylene groups of N–CH_2–CH_2 fragment. In the ^{13}C NMR spectrum the signals of the CH_2–CH_2–C(O)–CH_3 moiety were observed at 45.0 (d, $^{2}J_{C,P}$=11.6 Hz), 38.1 (d, $^{3}J_{C,P}$=2.2 Hz), 207.7 (s) and 30.2 (s) ppm, respectively.

Table 2 and Fig.2 show the ^{1}H NMR monitoring data for the reaction between **5a**, PPh_3 (1 equiv.) and CS_2 at 25 °C in a mixture of $CDCl_3$–CS_2. Under these conditions, the rate of the

formation of compound **8a** was rather low. After 39 min, azide **5a**, isothiocyanate **8a**, iminophosphorane **7a** and methyl vinyl ketone **6a** in a 38:45:10:7 ratio were observed. After 4 h, the amount of isothiocyanato **8a** increased to 62 %. Two unidentified products (or intermediates) were also formed in the reaction; however, the overall amount of these products did not exceed 15 %.

Table 2. Reaction of **5a** with PPh_3 and CS_2 ($CDCl_3$, 25 °C)[a]: dependence of the products distribution on the reaction time

Time (min)	Products distribution (%)			
	5a	**8a**	**7a**	**6a**
6	83	11	5	1
10	69	21	7	3
15	60	28	8	4
39	38	45	10	7
77	27	54	11	8
254	18	62	12	8
372	18	63	11	8

[a] A solution of PPh_3 (81.1 mg, 0.309 mmol) in 0.3 cm^3 $CDCl_3$ was added at once to a 5 mm NMR tube charged with a solution of **5a** (34.2 mg, 0.302 mmol) in 0.3 cm^3 CS2. The solution obtained was shaken carefully (gas evolution!). The progress of the reaction was monitored by ^1H NMR spectroscopy (Bruker DPX-300).

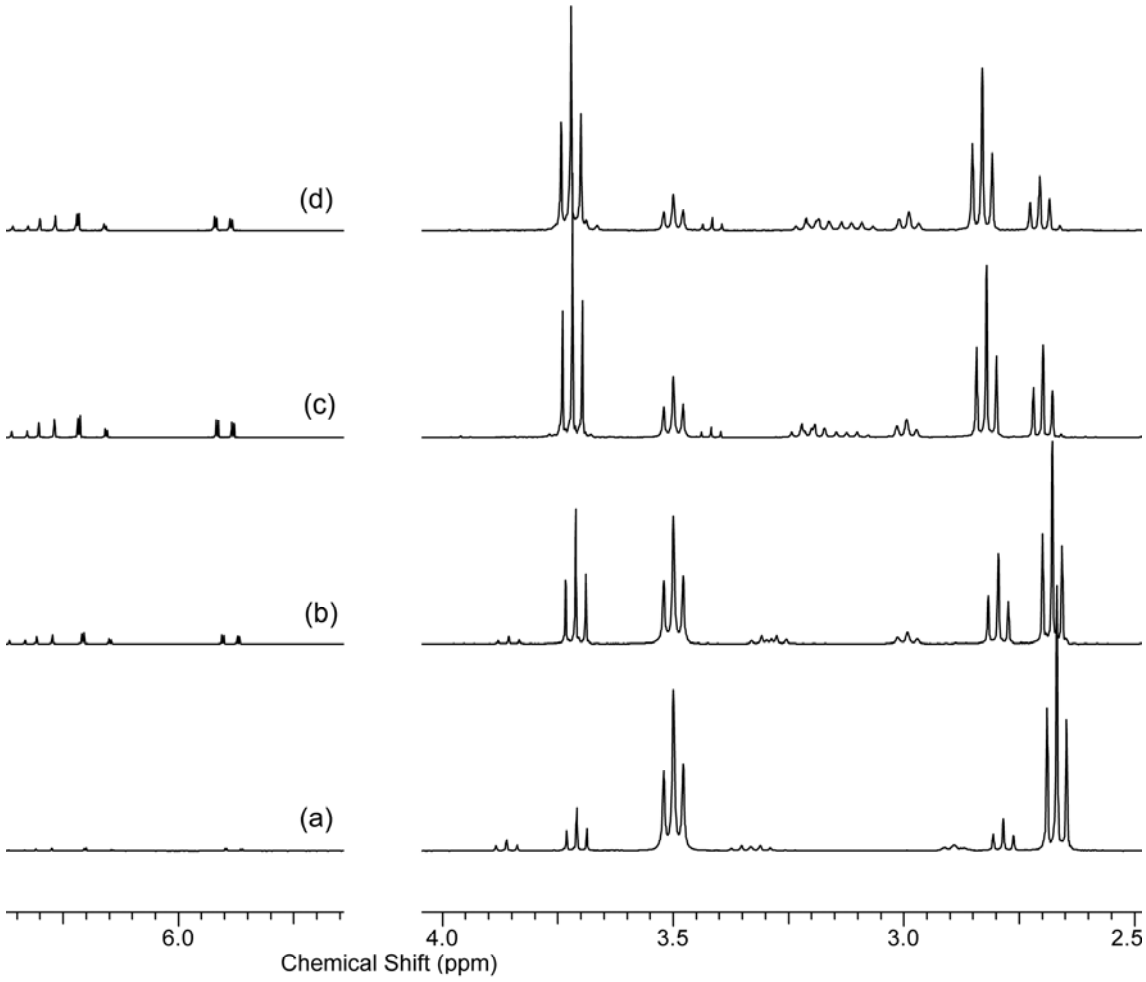


Fig. 2 a–d ^{1}H NMR spectra for the reaction of **5a** with PPh_3 and CS_2 ($CDCl_3$, 25 °C) after 6, 15, 77 and 254 min, respectively

Compared with the literature method [1–3, 18, 19], the above-described two-step methodology allows obtaining β-unsubstituted β-isothiocyanato ketones from α,β-unsaturated ketones with full chemoselectivity. The prepared isothiocyanates **8a–8c** were free from the corresponding isomeric thiocyanates **4**, whereas the previously described **8a, 8b** [35] were mixtures of the β-isothiocyanato and β-thiocyanato ketones in ratios of 50:50 and 65:35, respectively [21].

3. Conclusions

The present work demonstrates that a novel chemoselective two-step approach to β-isothiocyanato ketones starting from α,β-unsaturated ketones was developed. The synthesis involved preparation of β-azido ketones followed by reaction with triphenylphosphine and carbon disulfide. This approach was especially useful for synthesis of β-unsubstituted β-isothiocyanato ketones, which cannot be prepared with sufficient purity by commonly used procedures.

4. Acknowledgements

This work was supported by Russian foundation for basic research No. 12-03-31853 and the Presidential grant for young scientists No. MK-2956.2013.3.

5. References and notes

1. Bruson H.A. (**1946**) β-Thiocyano ketones and method for their preparation. *US Patent* 2,395,453, *Chem Abstr* 40:3467;
2. Verma R.P. (**2003**) *Phosphorus. Sulfur Silicon Relat Elem* 178:365;
3. Sondhi S.M., Singh N., Rajvanshi S. (**2004**) *Monatsh Chem* 135:119;
4. Mathes R.A., Stewart F.D., Swedish F. (**1948**) *J Am Chem Soc* 70:1452;
5. Ignatova L.A., Shutalev A.D., Shingareeva A.G., Dymova S.F., Unkovskii B.V. (**1985**) *Chem Heterocycl Compd* 21:218;
6. Shutalev A.D., Komarova E.N., Pagaev M.T., Ignatova L.A. (**1993**) *Chem Heterocycl Compd* 29:1077
7. Fisyuk A.S., Peretokin A.V., Ryzhova E.A., Boiko I.P., Unkovskii B.V. (**1996**) *Chem Heterocycl Compd* 32:732
8. Unkovskii B.V., Ignatova L.A. (**1969**) *Chem Heterocycl Compd* 5:667;
9. Fisyuk A.S., Ryzhova E.A., Unkovskii B.V. (**1994**) *Chem Heterocycl Compd* 30:238;
10. Zigeuner G., Lintschinger W.B., Fuchsgruber A., Kollmann K. (**1976**) *Monatsh Chem* 107:155;
11. Shutalev A.D., Zavodnik V.E., Gurskaya G.V. (**2000**) *Nucleos Nucleot Nucleic Acids* 19:1831;

12. Shutalev A.D., Ignatova L.A., Unkovskii B.V. (**1984**) *Chem Heterocycl Compd* 20:201;

13. Cho M.S., Lee I.S., Kang S.H., Kim Y.H. (**2005**) *Chem Eur J* 11:1452;

14. Zigeuner G., Fuchsgruber A., Wede F. (**1975**) *Monatsh Chem* 106:1495;

15. Zigeuner G., Lintschinger W.B., Fuchsgruber A., Kollmann K. (**1976**) *Monatsh Chem* 107:171;

16. Zigeuner G., Kollmann K., Lintschinger W.B., Fuchsgruber A. (**1976**) *Monatsh Chem* 107:183;

17. Singh H., Kumar S. (**1987**) *Tetrahedron* 43:2177;

18. Bhanot O.S., Ralhan N.K., Narang K.S. (**1964***)* *Indian J Chem* 2:238;

19. Unkovskii B.V., Ignatova L.A., Zaitseva M.G. (**1969**) *Chem Heterocycl Compd* 5:662;

20. Fierz G., McGarrity J.F., Dahn H. (**1975**) *Helv Chim Acta* 58:1058;

21. Peretokin A.V., Shutalev A.D., Chupin V.V., Mergenova A.M., Ignatova L.A., Malina Yu.F., Unkovskii B.V. (**1985**) *Russ. J Org Chem* 21:912;

22. Boyer J.H. (**1951**) *J Am Chem Soc* 73:5248;

23. Davies A.J., Donald A.S.R., Marks R.E. (**1967**) *J Chem Soc C* 1967:2109;

24. Gololobov Y.G., Zhmurova I.N., Kasukhin L.F. (**1981**) *Tetrahedron* 37:437;

25. Barluenga J., Palacios F. (**1991**) *Org Prep Proced Int* 23:1;

26. Gololobov Y.G., Kasukhin L.F. (**1992**) *Tetrahedron* 48:1353;

27. Wamhoff H., Richardt G., Stolben S. (**1995**) *Adv Heterocycl Chem* 64:159;

28. Fresneda P.M., Molina P. (**2004**) *Synlett* 1;

29. Palacios F., Alonso C., Aparicio D., Rubiales G., de los Santos J.M. (**2007**) *Tetrahedron* 63:523;

30. Banert K., Hagedorn M., Muller A. (**2001**) *Eur J Org Chem* 2001:1089;

31. Dem'yachenko E.A., Fesenko A.A., Dobretsova E.K., Fedorova G.A., Shutalev A.D. (**2010**) *Chem Heterocycl Compd* 46:631;

32. Singh P.N.D., Muthukrishnan S., Murthy R.S., Klima R.F., Mandel S.M., Hawk M., Yarbrough N, Gudmundsdottir A.D. (**2003**) *Tetrahedron Lett* 44:9169;

33. Jingliang J., Nguyen L.X., Patterson D.R., Flowers R.A. II (**2007**) *Org Lett* 9:1323;

34. Eguchi S., Takeuchi H., Esaki T. (1987) *Nippon Kagaku Kaishi* 1250; (**1988**) *Chem Abstr* 108:186470;

35. Unkovskii B.V., Ignatova L.A., Donskaya M.M., Zaitseva M.G. (**1965**) *Probl Organ Sinteza, Akad Nauk SSSR, Otd Obshch i Tekhn Khim* 202; (**1966**) *Chem Abstr* 64:9719a.