Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

One-Pot Synthesis of Acetoxyisothiocyanates Using Acetic Anhydride

Koji Hara [a] & Hirokuni Tajima [a]
[a] Fukui Research Laboratory, RENGO Co., Ltd. , 10--8--1, Jiyugaoka, Kanazu-cho, Sakai-gun, Fukui, 919--0604, Japan
Published online: 04 Dec 2007.

To cite this article: Koji Hara & Hirokuni Tajima (2000) One-Pot Synthesis of Acetoxyisothiocyanates Using Acetic Anhydride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:1, 141-146, DOI: 10.1080/00397910008087301

To link to this article: http://dx.doi.org/10.1080/00397910008087301

SYNTHETIC COMMUNICATIONS, 30(1), 141–146 (2000)

One-Pot Synthesis of Acetoxyisothiocyanates Using Acetic Anhydride

Koji Hara* and Hirokuni Tajima
Fukui Research Laboratory, RENGO Co., Ltd.,
10-8-1, Jiyugaoka, Kanazu-cho, Sakai-gun, Fukui 919-0604, Japan

Abstract: Acetoxyisothiocyanates were prepared by a one-pot synthesis from aminoalcohol, carbon disulfide and acetic anhydride.

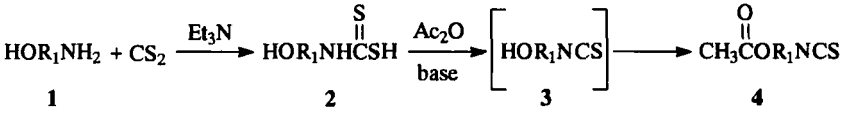
Conventional isothiocyanates[1,2] such as allyl and methyl isothiocyanate are used as antimicrobials, though their strong irritating odor limits their application areas. Recently, we have reported the synthesis of odorless isothiocyanates, hydroxyisothiocyanates[3,4]. Hydroxyisothiocyanates exhibited high antimicrobial activity[5] against some fungus and bacteria. However, due to their low volatility the antimicrobial activity was very low in gaseous contact. In order to overcome this shortcoming while keeping them odorless, we modified them through acetylation.

We wish to report in this work a one-pot synthesis of acetoxyisothiocyanates from aminoalcohol, carbon disulfide and acetic anhydride. Although the synthesis of isothiocyanate[6] through the decomposition of 1,3-disubstituted thiourea by acetic anhydride is known, the mechanism[7] differs from ours significantly.

---

*To whom correspondence should be addressed.

We first tried to convert 4-aminobutanol (**1a**) to 4-acetoxybutyl isothiocyanate (**4a**) (Scheme 1). According to our previous experiments[3,4], ordinary aliphatic hydroxydithiocarbamic acids (**2**) were obtained in quantitative yields after 1 h reaction of aminoalcohol with excess carbon disulfide in the presence of base. Therefore, for all the following experiments dithiocarbamation was carried out for 1 h unless otherwise stated and the reaction between acetic anhydride and the hydroxydithiocarbamic acid was mainly considered.



Scheme 1

It was found, by monitoring the reaction process with HPLC, that 4-hydroxybutyl isothiocyanate (**3a**) was generated in a quantitative yield immediately after both acetic anhydride and triethylamine were added to 4-hydroxybutyldithiocarbamic acid (**2a**) in dioxane. However, the following acetylation of **3a** to **4a** was much slower. For example, the yield of **4a** was only 33 % after 5 h. By employing 1,4-diazabicyclo[2.2.2]octane (DABCO), an efficient reagent for base-catalyzed acetylation[8], the yield of **4a** was raised up to 78 % after 90 min. Aliphatic acetoxyisothiocyanates were prepared by adding acetic anhydride and DABCO to the hydroxydithiocarbamic acid in dioxane and the results are listed in Table 1.

However, aromatic acetoxyisothiocyanates, *p*-acetoxyphenyl isothiocyanate (**4i**), was obtained only in 5 % yield under the same conditions. Again by monitoring the reaction process with HPLC, it was found that **4i** was generated in

Table 1. Synthesis of Aliphatic Acetoxyisothiocyanates Using DABCO in Dioxane[a]

entry	product	R_1	yield %
1	**4a**	$(CH_2)_4$	68
2	**4b**	$(CH_2)_5$	66
3	**4c**	$(CH_2)_6$	70
4	**4d**	$(CH_2)_2O(CH_2)_2$	78
5	**4e**[b]	$[(CH_2)_2]_2N(CH_2)_3$	60
6	**4f**	*trans*-4-cyclohexyl	48

[a] reactions were carried out for 90 min at room temperature
[b] **4e**: 3-(*N,N*-Diacetoxyethyl)aminopropyl Isothiocyanate

59 % yield 2 min after both acetic anhydride and DABCO were added. Nevertheless the yield of **4i** decreased rapidly due to side reactions between **4i** and by-products, thioacetic acid and acetic acid, to give *p*-acetoxyphenylacetamide. The quick formation of **4i** would be attributed to the high nucleophilicity of phenol to acetic anhydride. By using water and triethylamine as the reaction medium and the base, respectively, the yield of **4i** was raised up to 67 % after 2 min. The solvent effect was probably that the phase separation reduced the side reactions between the oil-soluble **4i** and the water-soluble by-products. Aromatic acetoxyisothiocyanates were thus prepared by adding acetic anhydride and triethylamine to the hydroxydithiocarbamic acid in water. It is known that prolonging the dithiocarbamation time[9] could increase the isothiocyanate yield when the lower basicity amine, such as aromatic amine, was used as the starting material. As seen from Table 2, the yields of both **4i** and *m*-acetoxyphenyl isothiocyanate (**4h**) increased by extending the dithiocarbamation time. On the other hand, it lowered the yield of *o*-acetoxyphenyl isothiocyanate (**4g**), although the reason is not clear at present.

Table 2. Synthesis of Aromatic Acetoxyisothiocyanates Using Triethylamine in Water[a]

entry	product	R_1	dithiocarbamation time[b] h	yield %
1	**4g**	*o*-C_4H_4	1	54
2	**4g**	*o*-C_4H_4	5	47
3	**4h**	*m*-C_4H_4	1	39
4	**4h**	*m*-C_4H_4	5	62
5	**4i**	*p*-C_4H_4	1	67
6	**4i**	*p*-C_4H_4	5	71

[a] reactions were carried out for 2 min at room temperature
[b] dithiocarbamation time: Time for the reaction of amine with carbon disulfide in the presence of triethylamine

Experimental Section

General Methods. All solvents and reagents obtained from commercial sources were used without further purification. NMR spectra were measured in $CDCl_3$ with tetramethylsilane and $CDCl_3$ as the internal standard for ^1H (270 MHz) and ^{13}C (22.4 MHz), respectively.

General procedure for the aliphatic acetoxyisothiocyanates 4a-4f. To a solution of **1** (20 mmol) and triethylamine (20 mmol) in dioxane (50 mL) was added carbon disulfide (60 mmol). After being stirred for 1 h at room temperature, acetic anhydride (44 mmol) and DABCO (20 mmol) were again added to the mixture. After the mixture was stirred for another 90 min at room temperature, ether was added and the organic layer was washed with 5% ammonia solution and water. The organic layer was dried and concentrated. The residue was subjected to column chromatography to give the pure product.

4-Acetoxybutyl Isothiocyanate (4a). Hexane:EtOAc (8:2) was used as the eluent: IR (neat) 2184-2109 (ν_{NCS}), 1738 ($\nu_{C=O}$) cm^{-1}; ^1H NMR δ 1.77-1.80 (m, 4H), 2.06 (s, 3H), 3.60 (t, 2H, J = 6.2 Hz), 4.11 (t, 2H, J = 5.9 Hz); ^{13}C NMR δ 20.69, 25.52, 26.47, 44.49, 63.06, 129.99, 170.69; MS m/z (M^+) 173. Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.40; N, 8.09; S, 18.51. Found: C, 48.18; H, 6.37; N, 7.94; S, 18.32.

5-Acetoxypentyl Isothiocyanate (4b). Hexane:EtOAc (8:2) was used as the eluent: IR (neat) 2182-2106 (ν_{NCS}), 1738 ($\nu_{C=O}$) cm^{-1}; ^1H NMR δ 1.47-1.80 (m, 6H), 2.06 (s, 3H), 3.55 (t, 2H, J = 6.8 Hz) 4.08 (t, 2H, J = 6.5 Hz); ^{13}C NMR δ 20.76, 22.88, 27.64, 29.36, 44.73, 63.69, 129.83, 170.85; MS m/z (M^+) 187.

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48; S, 17.12. Found: C, 50.96; H, 6.92; N, 7.26; S, 17.05.

6-Acetoxyhexyl Isothiocyanate (4c). Hexane:EtOAc (7:3) was used as the eluent: IR (neat) 2180-2106 (ν_{NCS}), 1737 ($\nu_{C=O}$) cm^{-1}; ^1H NMR δ 1.40-1.75 (m, 8H), 2.05 (s, 3H), 3.53 (t, 2H, J = 6.8 Hz) 4.07 (t, 2H, J = 6.8 Hz); ^{13}C NMR δ 20.86, 25.16, 26.15, 28.30, 29.74, 44.85, 64.12, 129.79, 171.01; MS m/z (M^+) 201. Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96; S, 15.93. Found: C, 53.74; H, 7.52; N, 6.84; S, 15.80.

2-(2-Acetoxyethoxy)ethyl Isothiocyanate (4d). CH_2Cl_2:acetone (9:1) was used as the eluent: IR (neat) 2202-2115 (ν_{NCS}), 1739 ($\nu_{C=O}$) cm^{-1}; ^1H NMR δ 2.10 (s, 3H), 3.71-3.75 (m, 6H), 4.23 (t, 2H, J = 4.6 Hz); ^{13}C NMR δ 20.52, 44.87, 62.88, 68.73, 132.22, 170.46; MS m/z (M^+) 189. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86; N, 7.40; S, 16.94. Found: C, 44.45; H, 5.85; N, 7.36; S, 16.67.

3-(*N,N*-Diacetoxyethyl)aminopropyl Isothiocyanate (4e). acetic anhydride (66 mmol) and DABCO (40 mmol) were added to the mixture. CH_2Cl_2:acetone (9:1) was used as the eluent: IR (neat) 2184-2111 (ν_{NCS}), 1739 ($\nu_{C=O}$) cm^{-1}; ^1H NMR δ 1.77-1.86 (m, 2H), 2.06 (s, 6H), 2.67 (t, 2H, J = 6.5 Hz), 2.77 (t, 4H, J = 5.9 Hz), 3.62 (t, 2H, J = 6.8 Hz), 4.11 (t, 4H, J = 5.9 Hz); ^{13}C NMR δ 20.79, 28.16, 42.48, 51.32, 52.76, 62.27, 129.94, 170.73; MS m/z (M^+) 288. Anal. Calcd for $C_{12}H_{20}N_2O_4S$: C, 49.98; H, 6.99; N, 9.71; S, 11.12. Found: C, 49.84; H, 6.91; N, 9.68; S, 11.11.

***trans*-4-Acetoxycyclohexyl Isothiocyanate (4f).** Hexane:EtOAc (7:3) was used as the eluent: IR (KBr) 2196-2142 (ν_{NCS}), 1726 ($\nu_{C=O}$) cm^{-1}; ^1H NMR δ 1.51-1.78 (m, 4H), 1.93-2.11 (m, 7H), 3.76-3.82 (m, 1H), 4.81-4.87 (m, 1H); ^{13}C NMR δ 21.17, 27.42, 29.31, 54.09, 69.67, 131.07, 170.22; MS m/z (M^+) 199. Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03; S, 16.09. Found: C, 54.00; H, 6.57; N, 6.95; S, 16.03.

General procedure for the aromatic acetoxyisothiocyanates 4g-4i. To a solution of **1** (20 mmol) and triethylamine (20 mmol) in water (50 mL) was added carbon disulfide (60 mmol). After being stirred for 1 h at room temperature, acetic anhydride (44 mmol) and triethylamine (20 mmol)were again added to the mixture. After the mixture was stirred for another 2 min at room temperature, ether was added and the organic layer was washed with 5% ammonia solution and water. The organic layer was dried and concentrated. The residue was subjected to column chromatography to give the pure product.

***o*-Acetoxyphenyl Isothiocyanate**[10] **(4g).** Hexane:EtOAc (7:3) was used as the eluent: IR (neat) 2055 (ν_{NCS}), 1775 ($\nu_{C=O}$) cm^{-1}; ^1H NMR δ 2.39 (s, 3H),

7.15-7.31 (m, 4H); ^{13}C NMR δ 20.56, 123.29, 124.96, 125.61, 126.60, 127.89, 140.54, 147.13, 168.48; MS m/z (M^+) 193.

***m*-Acetoxyphenyl Isothiocyanate**[11] **(4h).** Hexane:EtOAc (7:3) was used as the eluent: IR (neat) 2112 (ν_{NCS}), 1768 ($\nu_{C=O}$) cm^{-1}; ^{1}H NMR δ 2.29 (s, 3H), 6.98-7.36 (m, 4H); ^{13}C NMR δ 20.92, 119.17, 120.68, 123.06, 130.12, 132.11, 136.71, 151.05, 168.80; MS m/z (M^+) 193.

***p*-Acetoxyphenyl Isothiocyanate**[11] **(4i).** Hexane:EtOAc (7:3) was used as the eluent: IR (neat) 2186-2110 (ν_{NCS}), 1767 ($\nu_{C=O}$) cm^{-1}; ^{1}H NMR δ 2.29 (s, 3H), 7.07 (d, 2H, J = 8.9 Hz), 7.21 (d, 2H, J = 8.9 Hz); ^{13}C NMR δ 20.86, 122.73, 126.56, 128.61, 135.80, 149.11, 168.86; MS m/z (M^+) 193.

References

1. Delaquis, P. J. and Mazza, G. *Food Technol.*, **1995**, 73.
2. Fenwick, G. R.; Heaney, R. K.; Mulin, W. J. *Critical Reviews of Food Science and Nutrition*, **1983**, 18, 123.
3. Li, G.; Tajima, H.; Ohtani, T. *J. Org. Chem.*, **1997**, 62, 4539.
4. Tajima, H.; Li, G. *Synlett.*, **1997**, 7, 773.
5. Tajima, H.; Kimoto, H.; Taketo, Y.; Taketo, A. *Biosci. Biotechol. Biochem.*, **1998**, 62, 491.
6. Werner, E. A. *J. Chem. Soc.*, **1891**, 59, 396.
7. Baxter, J. N.; Cymerman-Craig, J.; Moyle, M.; White, R. A. *J. Chem. Soc.*, **1956**, 659.
8. Schenk, G. H.; Wines, P.; Mojzis, C. *Anal. Chem.*, **1964**, 36. 914.
9. Hodgkins, J. E.; Reeves, W. P.; Liu, Y. T. *J. Org. Chem.*, **1964**, 29, 3098.
10. Faull, A. W.; Hull, R. *J. Chem. Res., Synop.* **1979**, 5, 148.
11. Kristian, P.; Antos, J.; Kovac, S. *Chem. Zvesti.* **1963**, 17, 747.

(Received in Japan 19 April 1999)