Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8482–8486

The Michaelis–Arbuzov rearrangement of anomeric thiocyanates: synthesis and application of *S*-glycosyl thiophosphates, thiophosphonates and thiophosphinates as glycosyl donors

Marta Piekutowska and Zbigniew Pakulski*

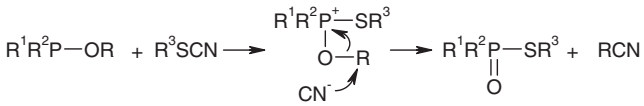
Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland

Received 27 July 2007; revised 17 September 2007; accepted 26 September 2007
Available online 29 September 2007

Abstract—Reaction of anomeric thiocyanates with triethyl phosphite, dimethyl phenylphosphonite and methyl diphenylphosphinite afforded the corresponding *S*-glycosyl thiophosphates, thiophosphonates and thiophosphinates in good yields. These derivatives were applied as glycosyl donors in the synthesis of benzyl glycosides and disaccharides with excellent stereoselectivity.

The Michaelis–Arbuzov reaction (also known as the Arbuzov reaction or Arbuzov rearrangement) is well known and widely used in general organic chemistry.[1] It results in pentavalent phosphorus derivatives with the formation of a new carbon–phosphorus bond. In most common form, the reaction usually requires prolonged heating at high temperature.

Due to their chemical properties,[2] thiocyanate derivatives (often classified as pseudohalogen derivatives) may also be considered as starting materials for the Michaelis–Arbuzov rearrangement. It has been demonstrated that alkyl and aryl thiocyanates are highly reactive reagents in the above reaction. The reaction involves S–CN bond fission and gives alkyl cyanates and *O*,*O*,*S*-trialkyl thiophosphates (Scheme 1).[3] Therefore, organic thiocyanates are potentially very promising substrates for the highly regioselective preparation of unsymmetrical *O*,*O*,*S*-trialkyl thiophosphates, however, examples of the Michaelis–Arbuzov reaction of organic thiocyanates are extremely rare.[4]



Scheme 1.

The effectiveness of glycosylation is a key problem in oligosaccharide synthesis and strongly depends upon the nature of the leaving group at the anomeric centre and its method of activation. Although numerous versatile leaving groups are known,[5] no single, universally applicable method for glycoside bond formation is available. The need for new, readily available, stable and reactive glycosyl donors still persists. During our studies directed towards the synthesis of oligosaccharides[6] we focused our attention on leaving groups containing a phosphorus atom. In this regard, anomeric thiocyanates[7,8] are particularly interesting starting materials for the preparation of anomeric thiophosphorus derivatives.

In this Letter, we report the preparation of *S*-glycosyl thiophosphates, thiophosphonates and thiophosphinates via Michaelis–Arbuzov reaction of glycosyl thiocyanates with simple phosphorus reagents. We have found that all the thiophosphorus derivatives obtained during this study act as excellent glycosyl donors forming *O*-glycoside bonds with excellent stereoselectivity. To our knowledge, thiophosphonates and thiophosphinates have never been used as glycosyl donors.

Glycosyl thiocyanates **1**–**5** (Fig. 1) were readily obtained by treatment of the corresponding glycosyl bromides

Keywords: Thiocyanates; Thiophosphates; Thiophosphonates; Thiophosphinates; Glycosyl donors; Glycosylation.
* Corresponding author. Tel.: +48 22 343 20 05; fax: +48 22 632 66 81; e-mail: pakul@icho.edu.pl

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.09.162

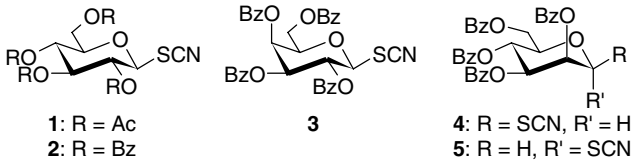


Figure 1.

with potassium thiocyanate in the presence of 18-crown-6 as described earlier.[7]

An initial Michaelis–Arbuzov reaction with tetra-*O*-acetyl glucose derived thiocyanate **1** was carried out in neat triethyl phosphite at 60 °C and afforded the expected thiophosphate **6** (Fig. 2) in low yield (20%). Acetylated glucosyl thiocyanate **1** was unstable at the high temperature required for reaction, hence we decided to use the more stable perbenzoylated thiocyanates **2**–**5** for further studies.[9]

Reaction of thiocyanate **2** with triethyl phosphite was performed at various temperatures. The highest yield of thiophosphate **7** (51%) was obtained at 120 °C. For some unknown reason, addition of a small amount of toluene as cosolvent practically stopped the reaction. Recent literature data[10] suggests that ionic liquids influence the Michaelis–Arbuzov reaction by increasing the yield and lowering the reaction temperature. However, in our hands, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) as solvent for the rearrangement of glycosyl thiocyanate **2** drastically reduced the yield of this reaction. It also promoted decomposition of the glycosyl thiocyanate, which resulted in contamination of the desired product with large amounts of inseparable sugar byproducts. A similar reaction was also performed with tributyl phosphite to afford thiophosphate **8**. The same reactions were performed for galactopyranosyl thiocyanate **3** and β-mannopyranosyl thiocyanate **4**. The expected glycosyl thiosphosphates **9**–**12** were obtained in moderate yields and the results are summarized in Table 1.

According to the ^{31}P NMR data the purity of thiophosphates **7**, **9** and **11** fluctuated between 77% and 99% and the products were contaminated with $H_2P(O)(OEt)$, $HP(O)(OEt)_2$ and $HOP(O)(OEt)_2$. The purities of compounds **8**, **10** and **12** were only 30–46%, byproducts including $HP(O)(OBu)_2$ and $HOP(O)(OBu)_2$ were formed.

The unique chemical properties of α-mannopyranosyl thiocyanate **5** should also be mentioned here. As we have observed previously, α-mannopyranosyl thiocyanate **5** was completely unreactive towards Grignard reagents.[7] This compound also remained stable during Michaelis–Arbuzov rearrangement, and we did not observe any reaction with triethyl phosphite, dimethyl

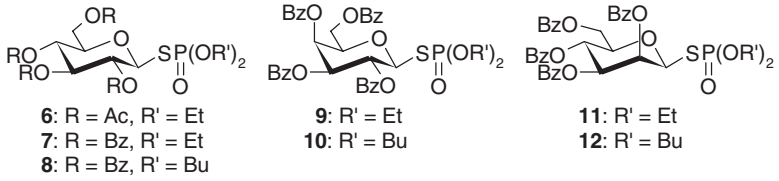


Figure 2.

Table 1. The Michaelis–Arbuzov rearrangement of glucosyl thiocyanates **2**–**4**

Entry	RSCN	$P(OR')_3$	Solvent or ionic liquid	Product	Temp. (°C)[a]	Time	Yield[b] (%)
1	**1**	$P(OEt)_3$	—	**6**	60	7 h	20
2	**2**	$P(OEt)_3$	—	**7**	20	24 h	26
3	**2**	$P(OEt)_3$	—	**7**	80	3 h	33
4	**2**	$P(OEt)_3$	—	**7**	120	30 min	51
5	**2**	$P(OEt)_3$	Toluene	**7**	110	18 h	Traces
6	**2**	$P(OEt)_3$	[bmim]BF_4	**7**	20	24 h	<10
7	**3**	$P(OEt)_3$	—	**9**	20	24 h	26
8	**3**	$P(OEt)_3$	—	**9**	80	2 h	30
9	**3**	$P(OEt)_3$	—	**9**	120	30 min	25
10	**3**	$P(OEt)_3$	[bmim]BF_4	**9**	60	4 h	Traces
11	**4**	$P(OEt)_3$	—	**11**	80	3.5 h	24
12	**2**	$P(OBu)_3$	—	**8**	80	24 h	22
13	**2**	$P(OBu)_3$	—	**8**	120	30 min	33
14	**3**	$P(OBu)_3$	—	**10**	60	8 h	25
15	**3**	$P(OBu)_3$	—	**10**	80	8 h	30
16	**4**	$P(OBu)_3$	—	**12**	80	4.5 h	30
17	**4**	$P(OBu)_3$	—	**12**	120	30 min	40

[a] Bath temperature.
[b] Purity was determined by ^{31}P NMR (161.9 MHz, $CDCl_3$) spectroscopy and the yield was calculated for pure product.

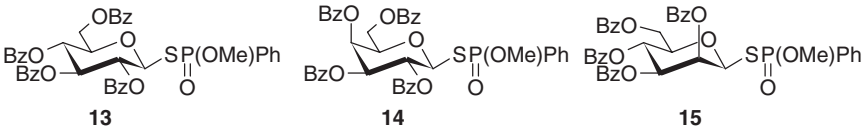


Figure 3.

Table 2. The Michaelis–Arbuzov rearrangement of glycosyl thiocyanates **2**–**4** with dimethyl phenylphosphonite $PhP(OMe)_2$

Entry	RSCN	Solvent or ionic liquid	Product	Temp. (°C)[a]	Time	Yield[b] (%)
1	**2**	—	**13**	40	30 min	51
2	**3**	—	**14**	40	30 min	53
3	**3**	[bmim]NTf_2	**14**	20	1 h	47
4	**4**	—	**15**	50	1 h	41

[a] Bath temperature.
[b] Purity was determined by ^{31}P NMR (161.9 MHz, $CDCl_3$) spectroscopy and the yield was calculated for pure product.

phenylphosphonite or methyl diphenylphosphinite. The reason for the unreactivity of α-mannopyranosyl thiocyanate **5** remains unknown, but we suspect that steric hindrance plays a role.

When dimethyl phenylphosphonite was used instead of triethyl phosphite in the reaction with glycosyl thiocyanates **2**–**4** under similar conditions, the expected *S*-glycosyl thiophosphonates **13**–**15** (Fig. 3) were obtained as an inseparable mixture of diastereoisomers in an approximate ratio of 1.2:1.0 in good yields. In this case, the purity of thiophosphonates **13**–**15** varied between 70% and 99%; HP(O)(Ph)(OMe) and HP(O)(Ph)(OH) were detected as contaminants by ^{31}P NMR. Here, [bmim]NTf_2 proved to be a suitable solvent for the above reaction (Table 2, entry 3). However, despite the relatively high reaction yield, it promoted a series of transformations of dimethyl phenylphosphonite affording a complex mixture of side products. The results are collected in Table 2.

Extension of these reaction conditions to methyl diphenylphosphinite as a starting material led to *S*-glycosyl thiophosphinates **16**–**18** (Fig. 4) in low yields. In this case, due to the instability of the final products at the higher temperatures, the reactions were conducted below 80 °C. Due to the high polarity, chromatographic separation of *S*-glycosyl thiophosphinates **16**–**18** was relatively simple and the purities of the products were usually higher than 95%. As side products, $Ph_2P(O)(OMe)$, $Ph_2P(OH)$ and $H_2P(O)(OMe)$ were detected with the aid of ^{31}P NMR. Detailed results are presented in Table 3.

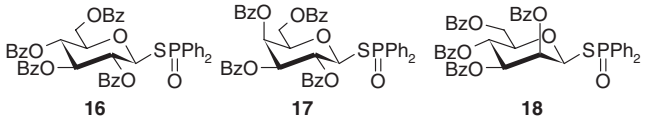


Figure 4.

It should be emphasized that in all the cases studied the configuration at the stereogenic centre connected to the sulfur atom (anomeric position) was fully preserved. Reactions were also regioselective affording *S*-glycosyl derivatives as the sole products.

Next, we focused on the use of thiophosphorus derivatives **7**–**17** as glycosyl donors. Prior work with *S*-glycosyl thiophosphates (very few analogues of such derivatives had been previously applied to carbohydrate chemistry[11]) suggested that thiophilic silver salts may serve as activators for such donors.[12] Unexpectedly, only traces of the desired products were detected upon reaction of **7** and benzyl alcohol (**19**) in the presence of silver triflate. We found that trimethylsilyl triflate was a convenient activating agent for all the donors tested. Preliminary results on glycosylations involving the use of donors **7**–**17** are outlined in Table 4. In all cases, this glycosylation method furnished exclusively the β-linked glycosides (for the *gluco* and *galacto* series) and the α-linked mannosides (Fig. 5). It is very important to note, that organophosphorus

Table 3. The Michaelis–Arbuzov rearrangement of glycosyl thiocyanates **2**–**4** with methyl diphenylphosphinite $Ph_2P(OMe)$

Entry	RSCN	Solvent or ionic liquid	Product	Temp. (°C)[a]	Time	Yield[b] (%)
1	**2**	—	**16**	40	30 min	20
2	**2**	—	**16**	80	10 min	25
3	**3**		**17**	rt	24 h	20
4	**3**	—	**17**	40	30 min	25
5	**3**	[bmim]NTf_2	**17**	20	30 min	Traces
6	**4**	—	**18**	50	3 h	Traces

[a] Bath temperature.
[b] Purity was determined by ^{31}P NMR (161.9 MHz, $CDCl_3$) spectroscopy and the yield was calculated for pure product.

Table 4. Glycosylation of benzyl alcohol ($C_6H_5CH_2OH$, **19**) and methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**20**) by donors **7**–**17**

Entry	Donor	Acceptor	Product	Yield (%)
1	**7**	**19**	**21**	80
2	**8**	**19**	**21**	40[a]
3	**13**	**19**	**21**	80
4	**16**	**19**	**21**	57
5	**9**	**19**	**22**	51
6	**10**	**19**	**22**	31[a]
7	**14**	**19**	**22**	70
8	**17**	**19**	**22**	53
9	**12**	**19**	**23**	67[a]
10	**15**	**19**	**23**	69
11	**7**	**20**	**24**	54
12	**13**	**20**	**24**	85
13	**9**	**20**	**25**	44
14	**14**	**20**	**25**	50
15	**17**	**20**	**25**	63
16	**15**	**20**	**26**	52

[a] Contaminated by organophosphorus byproducts.

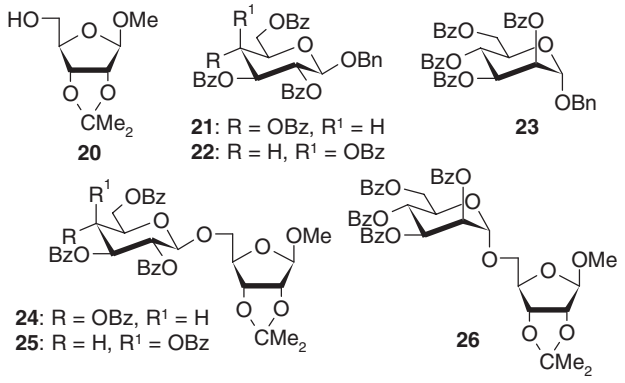


Figure 5.

impurities present in some donor samples did not influence the glycosylation process, and simple chromatographic separation afforded pure glycosides. The only exceptions were reactions involving dibutyl thiophosphates **8**, **10** and **12**, which gave the desired glycosides slightly contaminated with inseparable organophosphorus species.

In conclusion, we have developed an efficient synthesis of *S*-glycosyl thiophosphates, thiophosphonates and thiophosphinates from anomeric thiocyanates. The resulting *S*-glycosyl thiophosphates, thiophosphonates and thiophosphinates act as powerful glycosylation agents which, in the presence of TMSOTf as activator, install β-glucosidic, β-galactosidic and α-mannosidic linkages stereoselectively.

Acknowledgement

This work was supported by a Grant No. 3 TO9A 110 29 from the Ministry of Science and Higher Education, Poland.

References and notes

1. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.
2. Erian, A. W.; Sherif, S. M. *Tetrahedron* **1999**, *55*, 7957–8024.
3. (a) Michalski, J.; Wieczorkowski, J. *Bull. Acad. Pol. Sci. Cl. III* **1956**, *4*, 279–282; (b) Sheppard, W. A. *J. Org. Chem.* **1961**, *26*, 1460–1462; (c) Pilgram, K.; Phillips, D. D. *J. Org. Chem.* **1965**, *30*, 2388–2392.
4. (a) Ivanova, Z. M.; Kim, T. V.; Boldeskul, I. E.; Gololobov, Y. G. *Zh. Obsh. Khim.* **1979**, *49*, 1464–1470; (b) Cooper, D.; Trippett, S.; White, C. *J. Chem. Res. (S)* **1983**, 234–235; (c) Yarmukhamedova, D. K.; Shtyrlina, A. A.; Dubinina, N. P. *Zh. Obsh. Khim.* **1983**, *53*, 1755–1757; (d) Yarmukhamedova, D. K.; Gilmanova, G. K.; Buchin, P. I.; Cheplanova, I. V. *Khim. Pharm. Zh.* **1986**, *20*, 571–573; (e) Nuretdinova, O. N.; Novikova, V. G.; Troitskaja, L. B. *Izv. Akad. Nauk, Ser. Khim.* **1992**, 2673–2675; (f) Timperley, C. M.; Saunders, S. A.; Szpalek, J.; Waters, M. J. *J. Fluorine Chem.* **2003**, *119*, 161–171.
5. (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531; (b) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624.
6. (a) Nepogodev, S. A.; Pakulski, Z.; Zamojski, A.; Holst, O.; Brade, H. *Carbohydr. Res.* **1992**, *232*, 33–45; (b) Pakulski, Z. *Synthesis* **2003**, 2074–2078; (c) Pakulski, Z. *Polish J. Chem.* **2005**, *79*, 361–367; (d) Blattner, R.; Furneaux, R. H.; Pakulski, Z. *Carbohydr. Res.* **2006**, *341*, 2115–2125.
7. Pakulski, Z.; Pierożyński, D.; Zamojski, A. *Tetrahedron* **1994**, *50*, 2975–2992.
8. (a) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Tetrahedron Lett.* **1989**, *30*, 5459–5462; (b) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Bioorg. Khim.* **1990**, *16*, 701–710; (c) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Dokl. Akad. Nauk SSSR* **1991**, *321*, 1203–1207; (d) Kochetkov, N. K.; Malysheva, N. N.; Klimov, E. M.; Demchenko, A. V. *Dokl. Akad. Nauk SSSR* **1991**, *320*, 634–637; (e) Klimov, E. M.; Demchenko, A. V.; Malysheva, N. N.; Kochetkov, N. K. *Bioorg. Khim.* **1991**, *17*, 1660–1664; (f) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1991**, *212*, 77–91; (g) Kochetkov, N. K.; Malysheva, N. N.; Klimov, E. M.; Demchenko, A. V. *Tetrahedron Lett.* **1992**, *33*, 381–384; (h) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1992**, *232*, C1–C5; (i) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1993**, *242*, C7–C10.
9. *General procedure for the Michaelis–Arbuzov rearrangement*: A mixture of $P(OEt)_3$ (2–5 equiv) and thiocyanate **2** (1 equiv) was heated under an argon atmosphere in a screw cap tube (for product details see Tables 1–3). Column chromatography of the residue (hexane–ethyl acetate, 7:3) gave *S*-glycosyl phosphate **7**. ^1H, ^{13}C and ^{31}P NMR spectra were consistent with those expected for the structures assigned to the respective compounds. All compounds gave satisfactory high resolution mass spectra. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 22.4 (**6**), 22.6 (**7**), 22.8 (**8**), 22.9 (**9**), 23.1 (**10**), 23.2 (**11**), 23.4 (**12**), 42.9 and 41.1 (**13**), 42.7 and 41.3 (**14**), 43.1 and 41.1 (**15**), 42.4 (**16**), 42.4 (**17**).
10. Matveeva, E. V.; Odinets, I. L.; Kozlov, V. A.; Shaplov, A. S.; Mastryukova, T. A. *Tetrahedron Lett.* **2006**, *47*, 7645–7648.
11. (a) Michalska, M.; Michalski, J.; Orlich, I. *Bull. Acad. Pol. Sci. Ser. Chim.* **1974**, *22*, 1053–1057; (b) Michalska, M.;

Michalski, J.; Orlich, I. *Tetrahedron* **1978**, *34*, 617–622; (c) Chmielewski, M.; BeMiller, J. N. *Carbohydr. Res.* **1981**, *96*, 73–78; (d) Lipka, P.; Michalska, M. *Carbohydr. Res.* **1983**, *113*, 317–320; (e) Kudelska, W. *Pol. J. Chem.* **1997**, *71*, 1548–1552; (f) Kudelska, W. *Z. Naturforsch.* **1998**, *53b*, 1277–1280; (g) Kudelska, W. *Carbohydr. Res.* **2000**, *329*, 687–691; (h) Kulesza, A.; Frank, C. G.; Aebi, M.; Vasella, A. *Helv. Chim. Acta* **2004**, *87*, 3106–3118; (i) Cipolla, L.; Redaelli, C.; Faria, I.; Nicotra, F. *J. Carbohydr. Chem.* **2006**, *25*, 163–171; (j) Knapp, S.; Ajayi, K. *Tetrahedron Lett.* **2007**, *48*, 1945–1949.

12. (a) Borowiecka, J. *Liebigs Ann. Recueil* **1997**, 2147–2150; (b) Borowiecka, J.; Stańczak, A. *Il Farmaco* **2001**, *56*, 257–262.