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APPLICATION OF OXIMES FOR THE TRANSFER OF A C-H FRAGMENT

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Abstract

We report here on the synthesis of *O*-dialkoxymethyloximes from the corresponding oximes and the appropriate trialkyl orthoformate. The products were applied as the sources of C-H fragment which was then transferred to the selected molecules.

As a part of our continuous efforts concerning the synthesis and applications of various selective reagents in organic chemistry [1–6] we would like to describe our results on *O*-alkylated oximes. We recently introduced hydrazides of aliphatic, aromatic and heteroaromatic acids as well as arylsulfonyl hydrazines as convenient carriers of a C-H fragment.[7,8] Those hydrazino derivatives were transformed either with triethyl orthoformate (TEOF) or with diethoxymethyl acetate to the corresponding hydrazones. The latter compounds were found to serve as sources of a C-H fragment when reacted with the appropriate substrates. Searching for the other carriers of C-H fragment, oximes seemed to be promising candidates to reach the same goal. Our investigation in this direction is reported here. Dimethylglyoxime **1** and cyclohexanone oxime **2** were selected

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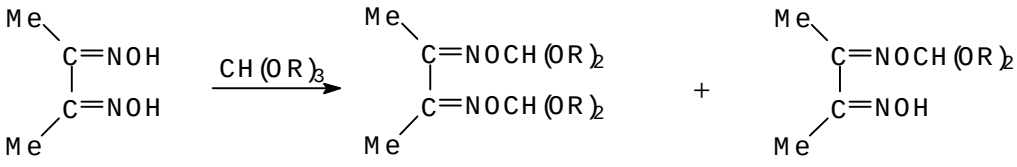
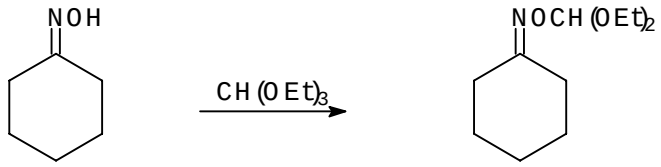
Dedicated to the memory of Professor Jože Šiftar.

as a stable, simple, cheap and commercially available starting materials. Thus, dimethylglyoxime **1** was heated under reflux with an excess of TEOF to give the mixture of *bis*-*O*-alkylated product **3a** and mono-*O*-alkylated analogue **3b**, the ratio being about 5:3 (Scheme 1). All attempts to obtain exclusively **3a** failed, even on prolonged heating with a large excess of TEOF. Similarly, **4a** and **4b** were prepared in the ratio of about 3:2 from **1** and trimethyl orthoformate (TMOF). Separation of the mixture **3a**/**3b** or **4a**/**4b** was performed by radial chromatography leading to pure **3a**, **3b**, **4a** and **4b**. Furthermore, cyclohexanone oxime **2** was treated with TEOF to give the corresponding derivative **5**.

Scheme 1



1 **3a** (R = Et) **4a** (R = Me) **3b** (R = Et) **4b** (R = Me)

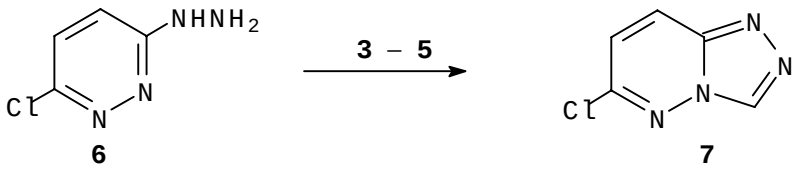


2 **5**

Our initial studies involved *bis*-*O*-alkylated oximes **3a** and **4a**, as well as mono-*O*-alkylated derivatives **3b**, **4b** and **5**, with the regard to their ability to transfer a C-H fragment to another molecule. It is well known that hydrazones can be prepared by exchange reactions of hydrazines with oximes.[9] One could have expected similar transformations of *O*-alkylated oximes with monosubstituted hydrazines, but it was not found to be the case. Although compounds **3**–**5** did react with 3-chloro-6-hydrazino-

pyridazine (**6**), the isolated products were not hydrazones but 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine (**7**) accompanied by the parent oxime **1** or **2**. It means that *O*-alkylated oximes **3**–**5** acted in fact as the carriers of a C-H fragment (Table 1). The reactivity of *bis*-*O*-alkylated dimethylglyoximes **3a** and **4a** with 3-chloro-6-hydrazino-pyridazine is similar to that of mono-*O*-alkylated derivatives **3b** and **4b**; the only difference being the number of C-H fragments (two or one), available for the transfer to **6**. The above observation indicates that a mixture of **3a**/**3b** or **4a**/**4b** may be used instead of pure reagents, so the separation of the products from the crude reaction mixtures is not required. This assumption was indeed supported by separate experiments.

Table 1. Reactions of *O*-Alkylated Oximes with **6**.



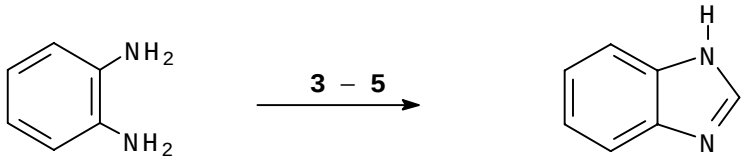
Entry	Reagent	Molar Ratio Reagent : **6**	Time (h)[a]	Yield of **7** (%)[b]
1	**3a**	0.57 : 1	3	58
2	**3b**	1.1 : 1	2.5	67
3	**4a**	0.53 : 1	4	63
4	**4b**	1 : 1	4.5	48
5	**5**	1 : 1	1.5	58

[a] Reactions were performed under reflux in 2-PrOH.
[b] Isolated yields are given.

The above results clearly show that *O*-alkylated oximes **3**–**5** can be applied as building blocks in the formation of 1,2,4-triazole ring. It was reasonable to use the same reagents in the construction of other rings, *e.g.* imidazole or oxazole. To do so, we performed ring closure of *o*-phenylenediamine (**8**) yielding benzimidazole (**9**). Initial attempts were carried out in refluxing ethanol and gave after the period of over 30 hours manly unchanged **8**, accompanied by small amounts of **9**. Better results were obtained

using DMF as a solvent (Table 2). It should be noted that diethoxymethylene derivatives **3a** or **3b** reacted faster than dimethoxymethylene analogues **4a** or **4b**. The reason is not well understood, but similar factor seems to play an important role also in the transformation of *o*-aminophenol (**10**) to benzoxazole (**11**).

Table 2. *O*-Alkylated Oximes Applied for the Synthesis of Benzimidazole (**9**).



8 **9**

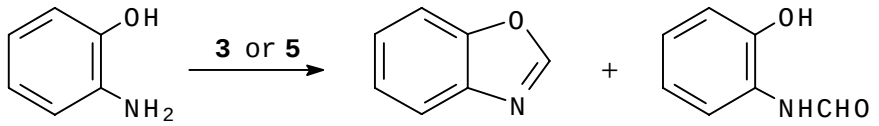
Entry	Reagent	Molar Ratio Reagent : **8**	Time (h)[a]	Yield of **9** (%)[b]
1	**3a**	0.5 : 1	3	77
2	**3b**	1.1 : 1	2.5	87
3	**4a**	0.5 : 1	15	46
4	**4b**	1 : 1	14	65
5	**5**	1 : 1	1.5	60

[a] Reactions were carried out under reflux in DMF.
[b] Isolated yields are given.

As it is evident from Table 3, a treatment of **10** with *O*-alkylated oximes **3a**, **3b** and **5** required more than 30 hours to give moderate yields of **11**. On the other hand, an application of reagents **4a** or **4b** on *o*-aminophenol under the same conditions led only to the traces of the expected products. Benzoxazole was always accompanied (entries: 1–3) by a certain amount of *o*-formylaminophenol. The latter compound seems to arise from the hydrolysis of *o*-diethoxymethylaminophenol, which is supposed to be the first product when the reagent attacks *o*-aminophenol. Although anhydrous ethanol was used as a solvent, a small amount of water, needed for the hydrolysis, was probably present in the reaction mixture. An alternative pathway for the formation of **12**, which would involve the addition of water to the position 2 of benzoxazole is unlikely under neutral conditions. On the contrary, thermal dehydration of *o*-acylaminophenols is the method

of choice for the preparation of benzoxazoles.[10] It is worth mentioning that all attempts to obtain **11** from **10** and reagents **3**–**5** in refluxing DMF resulted in complex mixtures and were not investigated further.

Table 3. Transformations of *o*-Aminophenol (**10**) with *O*-Alkylated Oximes.



10 **11** **12**

Entry	Reagent	Molar Ratio Reagent : **10**	Time (h)[a]	Yields of **11** and **12** (%)[b,c]
1	**3a**	0.58 : 1	31	34 (15)
2	**3b**	1.1 : 1	33	31 (9)
3	**5**	1.05 : 1	38	34 (19)

[a] Reactions took place under reflux in EtOH.
[b] Isolated yields are given.
[c] Yields of **12** are indicated in parenthesis.

In conclusion, we have described new carriers of C-H fragments, which were obtained from dimethylglyoxime or cyclohexanone oxime and TEOF or TMOF. Although new reagents **3**–**5** are less reactive than *N*-acylalkoxymethylene hydrazones,[7] they can be applied for the formation of either condensed 1,2,4-triazole or imidazole ring under neutral conditions.

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Experimental

Melting points were determined on a Kofler micro hot stage. NMR spectra were recorded on a Varian EM 360L instrument. IR spectra were obtained with Perkin-Elmer 727B and 1310 spectrometers. Elemental analyses (C, H, N) were performed with a Perkin-Elmer 2400 CHN Analyser. TLC was carried out on Fluka silica gel TLC plates (F_{254}). Column chromatography was performed on Fluka silica gel 60 (230–400 mesh). Radial Chromatography was carried out with a Harison Research instrument, model 7924 T, employing Merck silica gel 60 PF_{254}. 3-Chloro-6-hydrazinopyridazine (**6**) was prepared as described in the literature.[11] All other compounds were used without purification as obtained from commercial sources (Fluka, Merck, Aldrich). Isolated products: 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine (**7**),[12] benzimidazole (**9**),[13] benzoxazole (**11**)[14] and *o*-formylaminophenol (**12**),[14] were identical (IR, NMR, mp) with the compounds prepared following known procedures.

Reaction of Dimethylglyoxime with Triethyl Orthoformate.

A mixture of **1** (1 g) and TEOF (3 ml) was heated under reflux for 13 hours. The reaction mixture was evaporated to dryness and the residue separated by radial chromatography using petroleum ether : ethyl acetate (10 : 1) as a solvent to give *bis*-*O*-(diethoxymethyl)dimethylglyoxime (**3a**, 1.491 g, 54%) and *O*-(diethoxymethyl)dimethylglyoxime (**3b**, 0.559 g, 30%).

3a: mp 28 ºC; IR: 2990, 2940, 2910, 1450, 1375, 1335, 1145, 1110, 1050, 985, 930 cm^{-1}; NMR (60 MHz, $CDCl_3$, 24 ºC): δ 1.25 (t, 12H, J = 7 Hz), 2.1 (s, 6H), 3.7 (q, 8H, J = 7 Hz), 5.83 (s, 2H). Anal. Calcd for $C_{14}H_{28}N_2O_6$: C, 52.48; H, 8.81; N, 8.74. Found: C, 52.38; H, 9.02; N, 8.62.

3b: oil; IR: 3420, 2995, 2950, 2920, 1450, 1370, 1330, 1140, 1120, 1060, 970, 935 cm^{-1}; NMR (60 MHz, $CDCl_3$, 23 ºC): δ 1.3 (t, 6H, J = 7 Hz), 2.1 (s, 6H), 3.76 (q, 4H, J = 7 Hz), 5.86 (s, 1H), 8.5 (s, 1H). Anal. Calcd for $C_9H_{18}N_2O_4$: C, 49.53; H, 8.31; N, 12.84. Found: C, 49.51; H, 8.43; N, 13.13.

Reaction of Dimethylglyoxime with Trimethyl Orthoformate.

A mixture of **1** (1 g) and TMOF (7 ml) was heated under reflux for 42 hours. The reaction mixture was evaporated to dryness and the residue separated by radial chroma-

tography using petroleum ether : ethyl acetate (10 : 1) as a solvent to give *bis*-*O*-(dimethoxymethyl)dimethylglyoxime (**4a**, 1.043 g, 46%) and *O*-(dimethoxymethyl)dimethylglyoxime (**4b**, 0.597 g, 37%).

4a: mp 34 ºC; IR: 2935, 2840, 1445, 1365, 1330, 1220, 1200, 1140, 1110, 1050, 1010, 970, 910 cm^{-1}; NMR (60 MHz, $CDCl_3$, 23 ºC): δ 2.1 (s, 6H), 3.4 (s, 12H), 5.75 (s, 2H). Anal. Calcd for $C_{10}H_{20}N_2O_6$: C, 45.45; H, 7.63; N, 10.60. Found: C, 45.25; H, 7.58; N, 10.37.

4b: oil; IR: 3400, 2940, 2840, 1445, 1360, 1335, 1220, 1200, 1115, 1090, 1045, 980, 910 cm^{-1}; NMR (60 MHz, $CDCl_3$, 24 ºC): δ 2.1 (s, 6H), 3.45 (s, 6H), 5.75 (s, 1H), 8.5 (s, 1H). Anal. Calcd for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.73. Found: C, 43.81; H, 7.74; N, 14.32.

*Synthesis of Cyclohexanone O-Diethoxymethyloxime (**5**).*

A mixture of **2** (0.5 g) and TEOF (2.5 ml) was heated under reflux for 8 hours. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography using chloroform as a solvent to give *O*-(diethoxymethyl)cyclohexanone oxime (**5**, 0.594 g, 63%): oil; IR: 2970, 2920, 2850, 1445, 1370, 1320, 1170, 1100, 1075, 985, 935, 890 cm^{-1}; NMR (60 MHz, $CDCl_3$, 24 ºC): δ 1.25 (t, 6H, J = 7 Hz), 1.43–1.9 (m, 6H), 2.05–2.65 (m, 4H), 3.7 (q, 4H, J = 7 Hz), 5.73 (s, 1H). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 60.99; H, 9.65; N, 6.37.

*Typical Procedure for the Formation of 6-Chloro-1,2,4-triazolo[4,3-b]pyridazine (**7**).*

A mixture of the reagent **3a** (378 mg) and 3-chloro-6-hydrazinopyridazine (**6**, 344 mg) in 2-propanol (4 ml) was refluxed for 3 hours. Reaction mixture was then kept at 0 ºC for 1 hour, the solid material was filtered off and treated with chloroform (15 ml) to give unsoluble dimethylglyoxime (90 mg, 46%). Chloroform solution was evaporated to dryness yielding 6-chloro-1,2,4-triazolo[4,3-b]pyridazine (**7**, 270 mg, 58%): mp 202–205 ºC; lit.[12] mp: 203.5 ºC.

*Typical Procedure for the Preparation of Benzimidazole (**9**).*

A solution of the reagent **3a** (200 mg) and *o*-phenylenediamine (**8**, 135 mg) in DMF (2 ml) was heated under reflux for 3 hours. Solvent was evaporated under reduced

pressure, the residue was treated with diethyl ether (2 ml) and the solid material was filtered off giving benzimidazole (**9**, 114 mg, 77%): mp 172–173 ºC; lit.[13] mp: 170–172 ºC.

*Reaction of o-Aminophenol with **3** or **5**. A General Procedure.*

A solution of the reagent **5** (203 mg) and *o*-aminophenol (**10**, 98 mg) in anhydrous ethanol (2 ml) was heated under reflux for 38 h. Solvent was evaporated under reduced pressure and the products were separated by radial chromatography using petroleum ether : ethyl acetate (5 : 1) as the solvent: benzoxazole (**11**, 36 mg, 34%), mp 29 ºC, lit.[14] mp: 30–31 ºC; *o*-formylaminophenol (**12**, 23 mg, 19%), mp 127–129 ºC; lit.[14] mp: 129–129.5 ºC.

References

[1] M. Kočevar, P. Mihorko, S. Polanc, *Synlett* **1995**, 241–242.
[2] M. Kočevar, P. Mihorko, S. Polanc, *J. Org. Chem.* **1995**, *60*, 1466–1469.
[3] J. Košmrlj, M. Kočevar, S. Polanc, *Synlett* **1996**, 652–654.
[4] B. Štefane, M. Kočevar, S. Polanc, *J. Org. Chem.* **1997**, *62*, 7165–7169.
[5] V. Kepe, F. Požgan, A. Golobič, S. Polanc, M. Kočevar, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2813–2816.
[6] J. Košmrlj, M. Kočevar, S. Polanc, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3917–3919.
[7] M. Kočevar, P. Sušin, S. Polanc, *Synthesis* **1993**, 773–774.
[8] B. Košmrlj, B. Koklič, S. Polanc, *Acta Chimica Slovenica* **1996**, *43*, 153–162.
[9] J. S. Clark In *Comprehensive Organic Functional Group Transformations*; G. Pattenden, Ed.; Pergamon, Oxford, 1995; Vol. 3, pp 443–490.
[10] G. V. Boyd In *Comprehensive Heterocyclic Chemistry*; K. T. Potts, Ed.; Pergamon, Oxford, 1984; Vol. 6, pp 177–233.
[11] N. Takahayashi, *J. Pharm. Soc. Japan* **1955**, *75*, 778–781; *Chem. Abstr.* **1956**, *50*, 4970.
[12] N. Takahayashi, *J. Pharm. Soc. Japan* **1955**, *75*, 1242–1244; *Chem. Abstr.* **1956**, *50*, 8655.
[13] E. C. Wagner, W. H. Millett, *Organic Syntheses*; A. H. Blatt, Ed.; Wiley, New York, 1943; Coll. Vol. 2, pp 65–66.
[14] E. Bamberger, *Chem. Ber.* **1903**, *36*, 2042–2055.

Povzetek

Opisali sintezo *O*-dialkoksimetiloksimov iz ustreznih oksimov in primernih trialkil ortoformatov. Te produkte smo uporabili kot izvore CH fragmenta, ki ga je bilo mogoče prenesti na izbrane molekule.