Three-Component Synthesis of Some Novel *N*-Heterocycle Methyl-*O*-oxime Ethers

Mohammad Navid Soltani Rad,*[a] Somayeh Behrouz,*[a] Abdo Reza Nekoei,[a] Zeinab Faghih,[b] Ali Khalafi-Nezhad[b]

[a] Department of Chemistry, Shiraz University of Technology, Shiraz 71555-313, Iran
Fax +98(711)7354520; E-mail: soltani@sutech.ac.ir; E-mail: behrouz@sutech.ac.ir

[b] Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran

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Abstract: A convenient and highly efficient protocol for one-pot synthesis of some novel *N*-heterocycle methyl-*O*-oxime ethers is described. In this method, three-component coupling of different types of ketoximes, with methylene iodide and nitrogen heterocycles, including imidazoles, benzimidazole, benzotriazole, and theophylline in the presence of an equimolar mixture of K_2CO_3/Et_3N in refluxing MeCN furnished the corresponding *N*-heterocycle methyl-*O*-oxime ethers in good yields. This methodology is highly efficient for the synthesis of various structurally diverse *N*-heterocycle methyl-*O*-oxime ethers. The results of quantum mechanical studies on reaction intermediates are discussed.

Key words: three-component reaction (3CR), oxime, *O*-oxime ether, methylene iodide, N-heterocycle

Oximes and oxime ethers are important substrates in organic and medicinal chemistry.[1] They are a key structural motif in scaffolds of many drugs and bioactive compounds. Many famous drugs having different chemotherapeutic activities, such as antiviral (e.g., enviroxime),[2] anti-inflammatory (e.g., pifoxime),[1b] antibiotics (e.g., cefixime),[3] nerve antidotes (e.g., pralidoxime),[1b] antifungals (e.g., oxiconazole),[4] macrolide antibiotics (e.g., roxithromycin),[5] antidepressants (e.g., fluvoxamine),[1b] and thromboxane synthase inhibitors (e.g., ridogrel),[6] contain oxime and/or oxime ether bonds in their structure.

The multi-component reactions (MCRs) are one of the most important reactions in organic synthesis and medicinal chemistry.[7] The MCRs offer several attractive features to the chemical and pharmaceutical industries, including access to a large number of novel and diverse structures and lower production and environmental costs due to high convergence and a greater degree of atom economy. Many important reactions such as the Strecker,[8] Hantzsch,[9] Biginelli,[10] Mannich,[11] Passerini,[12] Ugi,[13] and Gewald[14] are well-known multi-component reactions. These reactions often involve condensation processes and ring closure. Indeed, there are only rare reports in which an S_N2 type reaction is a part of MCRs.[15]

Previously, we reported the synthesis of acycloaromatic nucleosides **1**,[15a,16] which led to introduction of 1-(phenoxymethyl)-6-azauracil (**2**) (Figure 1) as an active chemotherapeutic agents for inhibiting the growth of myeloid cell and useful in the treatment of leukemia.[17] In this context and also in continuation of our ongoing research on oxime chemistry,[15b,18] we report now a simple and highly efficient method for the synthesis of some novel *N*-heterocycle methyl-*O*-oxime ethers **3a–r** using three-component reaction (3CR) of oximes, methylene iodide, and nitrogen heterocycles in the presence of a K_2CO_3/Et_3N mixture in anhydrous MeCN at reflux condition (Scheme 1).

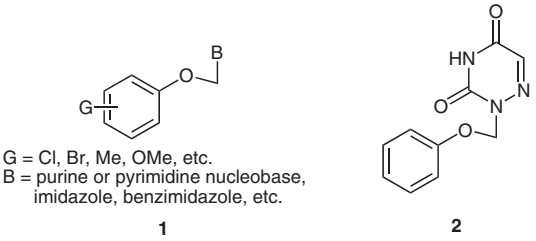
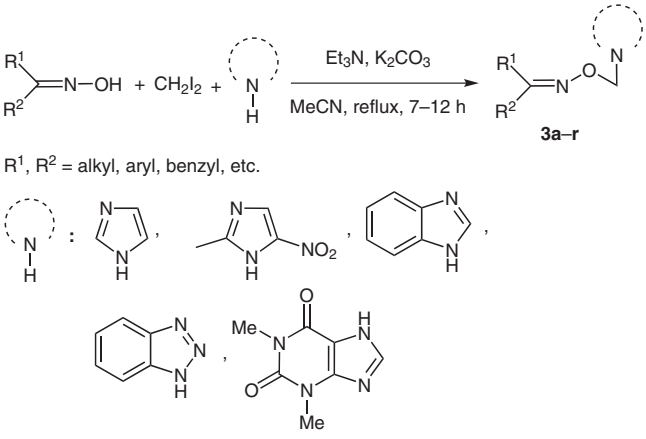


Figure 1 Acycloaromatic nucleosides **1** and 1-(phenoxymethyl)-6-azauracil (**2**)



Scheme 1

The first step of this synthetic approach involved optimization of the reaction conditions. Initially, the effect of various solvents on the reaction of benzophenone oxime, methylene iodide, and benzimidazole in the presence of an equimolar mixture of K_2CO_3/Et_3N was studied as a model reaction. The results are depicted in Table 1.

From Table 1, among the examined solvents, anhydrous MeCN (entry 4) afforded the best result and hence it was the used solvent for all reactions. In view of the fact that

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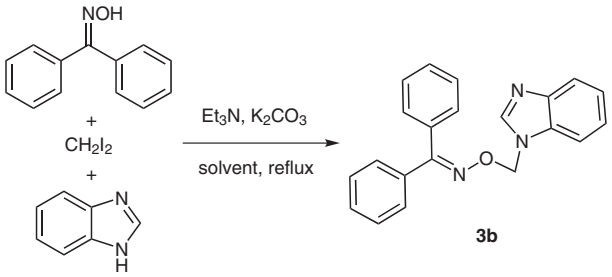
Table 1 Effect of Various Solvents on the Conversion of Benzophenone Oxime into **3b**



Entry	Solvent[a]	Time (h)	Yield (%)[b]
1	DMSO	12	56
2	DMF	9	58
3	MeCN	24	NR[c]
4	MeCN	7	68
5	HMPA	24	10
6	toluene	12	52
7	THF	12	48
8	acetone	9	60

[a] All solvents used were anhydrous.
[b] Isolated yield.
[c] No reaction. Wet MeCN was used.

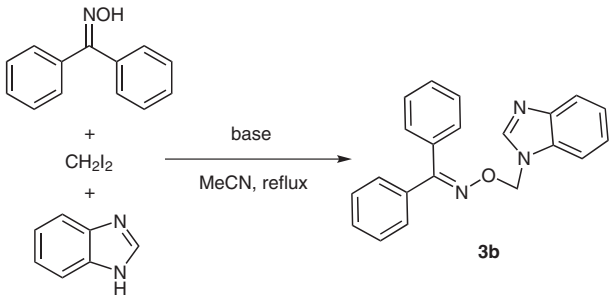
the generated reactive intermediates in the reaction mixture are very susceptible to the moisture, the use of an anhydrous solvent is critically essential. The explicit interference of moisture was easily observed by the comparison of results obtained by use of wet MeCN versus anhydrous sample (Table 1, entries 3 and 4).

Use of DMSO, DMF, and acetone (Table 1, entries 1, 2, and 8) afforded **3b** in moderate yields, whereas the other solvents were inefficient even if the reaction time was prolonged.

The choice of the reaction base for activation of the oximes and also the nitrogen heterocycle component to react with methylene iodide was found to have a great significance. In this case, the potency of several organic and inorganic bases on the reaction model was investigated (Table 2). Due to demonstrated results in Table 2, among the employed bases an equimolar mixture of K_2CO_3/Et_3N (entry 6) was the most efficient base for the progress of reaction. In addition, the attained yields by use of K_2CO_3 (1 equiv) (Table 2, entry 1) and/or Et_3N (2 equiv) (Table 2, entry 5) distinctly were not as efficient as an equimolar mixture of K_2CO_3/Et_3N. Use of Cs_2CO_3, DBN, and DBU (Table 2, entries 2, 7, and 8) also afforded **3b** in good yields, while the other bases were inefficient.

The optimized stoichiometric ratios of nitrogen heterocycle/CH_2I_2/oxime/K_2CO_3/Et_3N for the conversion of benzophenone oxime into **3b** were found to be one equivalent for each of the components.

Table 2 Effect of Various Bases on the Conversion of Benzophenone Oxime into **3b**



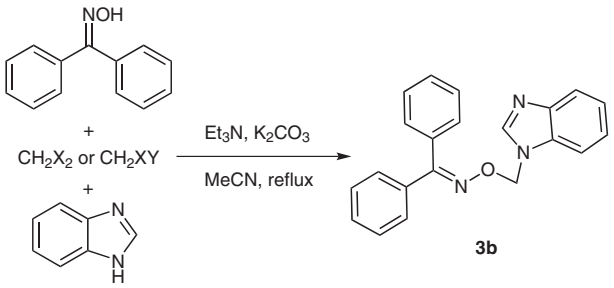
Entry	Base	Time (h)	Yield (%)[a]
1	K_2CO_3	7	65
2	Cs_2CO_3	7	65
3	NaH	8	53
4	MgO	24	NR[b]
5	Et_3N	24	27
6	K_2CO_3/Et_3N[c]	7	68
7	DBN	8	60
8	DBU	8	61
9	DABCO	24	NR[b]
10	DMAP	24	NR[b]

[a] Isolated yield.
[b] No reaction.
[c] 1:1 ratio.

To compare the capability of other dihalomethanes in progress of the reaction, the effect of various dihalomethane derivatives on model reaction was examined (Table 3). As the data in Table 3 indicate, the dichloromethane (Table 3, entry1) was not suitable for processing the reaction. This is due to the fact that dichloromethane exhibits the low boiling point (39.6 °C) that normally is evolved from the reaction mixture (i.e., refluxing MeCN). Though dibromomethane, chloroiodomethane, and bromoiodomethane (Table 3, entries 2, 4, and 6) were demonstrated to give moderate yields of **3b**, the bromochloromethane (Table 3, entry 5) provided a low yield of the product.

The scope of this method was evaluated by its extension to various structurally diverse oximes and nitrogen heterocycles (Table 4). Based on the data in Table 4, this method is applicable for various nitrogen heterocycles such as imidazole, benzimidazole, 2-methyl-4(5)-nitro-1*H*-imidazole, and theophylline. In addition, this method is suitable for all kinds of ketoximes, including aromatic, benzylic, aliphatic, alicyclic, and other ketoximes. Most of the oximes used in this research are commercially available or can be easily prepared according to the procedure reported in the literature.[19]

Table 3 Effect of Various Dihalomethanes on the Conversion of Benzophenone Oxime into **3b**



Entry	CH_2X_2 or CH_2XY[a]	Time (h)	Yield (%)[b]
1	CH_2Cl_2	24	NR[c]
2	CH_2Br_2	13	43
3	CH_2I_2	7	68
4	CH_2ClI	11	46
5	CH_2BrCl	16	21
6	CH_2BrI	10	52

[a] X, Y = Cl, Br, I.
[b] Isolated yield.
[c] No reaction.

Synchronous reaction of oxime with methylene iodide and nitrogen heterocycle is normally expected to give three products. In this synthetic methodology, *N*-heterocycle methyl-*O*-oxime ethers were obtained predominantly. However, other products were formed either by N-alkylation of the nitrogen heterocycles or O-alkylation of oximes with methylene iodide in trace amounts (<5%). MCRs can be used for domino reactions with inseparable intermediates or sequential reactions with separable intermediates.[20] It is worthy to note that the anticipated iodomethyl-*O*-oxime ether intermediate, which has the close resemblance with classic α-halo ethers, is quite unstable and cannot be separated by normal separation techniques. Consequently, the preparation of compounds **3a**–**r** cannot be achieved using stepwise synthesis and they must be merely synthesized via the three-component reaction (3CR).

Oximes are known to be ambident nucleophiles.[21] The alkylation of an oxime can be achieved either at the oxygen to afford *O*-alkyl ether or at the nitrogen to generate nitrones.[22] Similarly, other ambident nucleophiles, the site of alkylation in the oxime anion is affected by numerous factors, such as base and types of solvent, the nature of alkylating agents and cation, the geometry of the substrate, functional groups present on the oxime, and the degree of dissociation of the oxime salts.[22,23] Using the present method, the *O*-alkyl ethers were mainly obtained and no nitrones were detected, even in trace amounts.

Table 4 Three-Component Synthesis of *N*-Heterocycle Methyl-*O*-oxime Ethers Using Oximes, CH_2I_2, Nitrogen Heterocycles, K_2CO_3, Et_3N in Refluxing MeCN

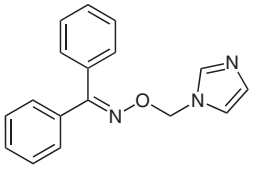
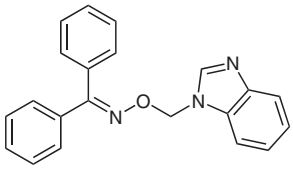
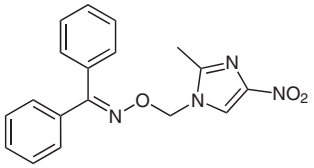
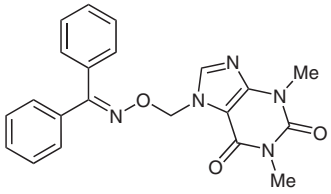
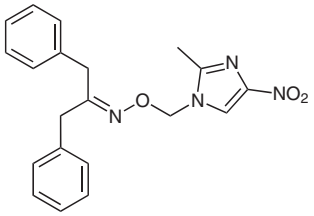
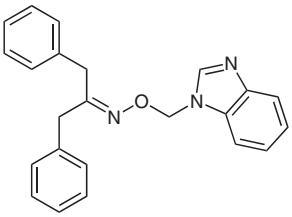
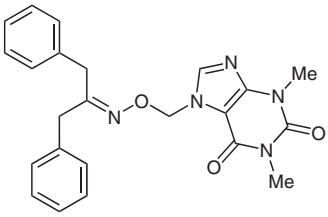
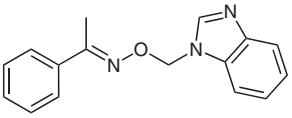
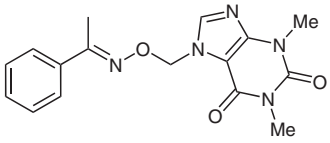
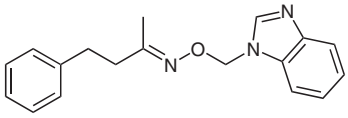
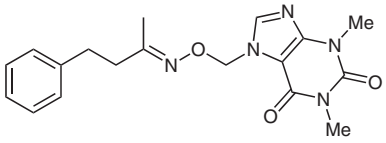
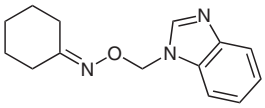
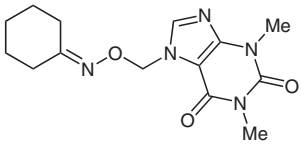
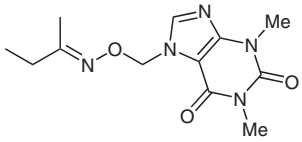
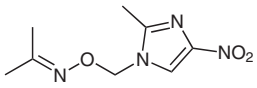
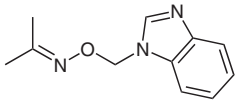
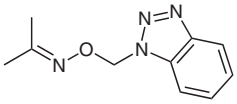
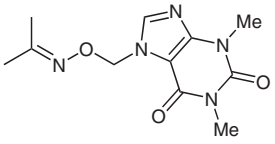
Product	Structure[a]	Time (h)	Yield (%)[b]
3a		7	70
3b		7	68
3c		11	82
3d		10	75
3e		12	60
3f		9	65
3g		8	72
3h		7	69

Table 4 Three-Component Synthesis of *N*-Heterocycle Methyl-*O*-oxime Ethers Using Oximes, CH_2I_2, Nitrogen Heterocycles, K_2CO_3, Et_3N in Refluxing MeCN (continued)

Product	Structure[a]	Time (h)	Yield (%)[b]
3i		8	74
3j		10	60
3k		8	70
3l		11	62
3m		9	70
3n		10	62
3o		8	68
3p		8	70
3q		7	73
3r		7	75

[a] All products were characterized by ^1H and ^{13}C NMR, IR, CHN, and MS analysis.
[b] Isolated yield.

In the case of 2-methyl-4(5)-nitro-1*H*-imidazole, which has proved to have the considerable medical and agricultural applications,[24] compounds **3c**, **3e**, and **3o** were synthesized accordingly. In agreement with the literature,[25,26] the N-alkylation of 2-methyl-4(5)-nitro-1*H*-imidazole with iodomethyl-*O*-oxime ether intermediates mainly afforded the respective 4-NO_2 isomers rather than 5-NO_2 isomers. Moreover, the N-alkylation reactions of theophylline and 1*H*-benzotriazole were also achieved regioselectively. Theophylline derivatives were obtained as the N7-isomers, while the 1*H*-benzotriazole was mostly alkylated at N1 atom affording **3q** in 73% yield.

Theoretical Aspect

It is well known that α-halo ethers (HE) are very sensitive to water, and they decompose to the corresponding alcohols and aldehydes, immediately:

$$RCH_2OCH_2X + H_2O \rightarrow RCH_2OH + CH_2O + HX$$

α-Halo-*O*-oxime ethers (HOEs), the intermediates in the present work, are the examples of more stable (in the other word, less unstable) α-halo ether compounds in comparison with classic (linear) α-halo ethers. In HOE, because of another resonance form of molecule (in which the lone-pair electrons of oxygen move toward nitrogen atom), the weakening of C–X bond (X as the halogen atom) is decreased. In α-halo ethers (HE), the anomeric effect, that is, the interaction between oxygen lone-pair orbital and antibonding sigma orbital associated with antiperiplanar C–X bond [$n_{(O)} \rightarrow \sigma^*_{(C-X)}$] causes the weakening of C–X bond. As the result, the HOEs are less unstable than linear HE intermediates, and could lead to the target products.

Quantum mechanical calculations by Gaussian 03W[27] and NBO 5.0 programs,[28] using DFT method at B3LYP/6-311G** level of theory, have been carried out on some HE and HOE molecules to investigate and compare their anomeric effects. For computational simplification, chlorine atom was selected as halogen in calculated molecules. Additionally, various R groups were investigated, since the R groups with different electronic properties have different influences on the anomeric effect (Figure 2). In order to evaluate the effect of phenyl substitution on HOE, the influence of the electron-withdrawing CF_3 and methyl groups has been selected for comparing.

The calculated results for some bond lengths, Wiberg bond orders (WBO), atomic natural charges, and second order perturbation energies of some donor-acceptor orbital interactions for selected compounds are given in Tables 5 and 6.

By comparing the selected bond lengths and WBOs for HE and HOE compounds in Table 5, it is concluded that the lone pair of oxygen atom in HOE molecules leans toward the N atom, therefore their O–C bond length is longer than the corresponding value in HE molecules. As the result of this electron charge dispersion, the C–X bond lengths are shorter and stronger in HOE compounds in such a way that in the presence of water they are more stable than classic HE and can be formed as reaction intermediates (e.g., this work).

These results are in best agreement with the calculated donor-acceptor orbital interaction energies and atomic natural charges in Table 6. The first entry in Table 6 shows the energy for $n_{(O)}$ to $\sigma^*_{(C-X)}$ orbital interaction in HEs and HOEs, which is directly related to the anomeric effect. It

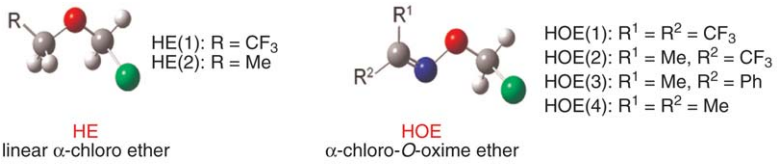


Figure 2 Selected α-halo and α-halo-*O*-oxime ethers with different substitutions

Table 5 Selected Bond Lengths in Å and Wiberg Bond Orders (WBO) Calculated at B3LYP/6-311G** Level of Theory

	α-Chloro-*O*-oxime ether				α-Chloro ether	
Bond length	HOE(1)	HOE(2)	HOE(3)	HOE(4)	HE(1)	HE(2)
N/C–O[a]	1.376	1.401	1.416	1.427	1.416	1.438
O–C	1.403	1.387	1.377	1.374	1.372	1.361
C–Cl	1.811	1.830	1.845	1.850	1.851	1.871
WBO						
N–O	1.041	0.994	0.971	0.956	0.911	0.875
O–C	0.925	0.955	0.980	0.989	0.988	1.020
C–Cl	1.004	0.979	0.954	0.947	0.950	0.923

[a] N–O bond length for HOEs and C–O bond length for HEs.

is obvious that the anomeric effect is significantly reduced in HOE compounds. Instead, another notable interaction of type $n_{(O)}$ to $\pi^*_{(C–N)}$ is detected in HOE molecules, whereas this type of interaction is absent in HE compounds.

All these data suggest that there is an electron delocalization from O atom toward R functional groups in HOEs (which is confirmed by atomic natural charges, Table 6). Also it is obvious that the phenyl and electron-withdrawing CF_3 groups in R positions can assist this delocalization and reduce the anomeric effect to more stabilize the HOE intermediates. Comparison between calculated data of HOE molecules with different R substituents shows that the phenyl influence on reducing anomeric effect is more than that of methyl group but less than that of CF_3 group. Because of steric hindrance, the phenyl group cannot be fully coplanar with C=N–O segment of molecule (CCCN dihedral angles are 45.5° for R^1 = Ph and R^2 = Me, and 18.6° for R^1 = Me and R^2 = Ph), and therefore has not remarkable resonance conjugation with this segment. That is why the phenyl group has less reducing role on the anomeric effect in comparison with CF_3 group. In addition, calculations for HOE(3) molecule show a donor-acceptor interaction of type $\pi_{(C–C)Ph} \rightarrow \pi^*_{(C–N)}$ (16.32 kcal/mol), which is an evidence for another direction of π-electron resonance conjugation from phenyl toward C=N–O part of molecule. This direction is in contrast with the way that weakens the anomeric effect.

In conclusion, a convenient and simple protocol is described for synthesis of novel *N*-heterocycle methyl-*O*-oxime ethers **3a–r** via three-component reaction (3CR) of oximes with methylene iodide and nitrogen heterocycles. The regioselectivity of the reaction, simple experimental procedure, mild reaction condition, and relatively high yields of products are advantages of this method. Finally, to rationalize the experimental outcomes, quantum mechanical studies on the basis of DFT method have been

Table 6 Selected Second Order Perturbation Energies $E^{(2)a}$ and Some Atomic Natural Charges

	α-Chloro-*O*-oxime ether				α-Chloro ether	
Parameter	HOE(1)	HOE(2)	HOE(3)	HOE(4)	HE(1)	HE(2)
LP(2) O1 to BD*(1) C–Cl	14.38	16.91	19.32	20.22	20.56	23.77
LP(2) O1 to BD*(2) C–N	22.66	16.58	13.46	12.29		
C charge	0.030	0.166	0.266	0.290		
N charge	–0.072	–0.129	–0.176	–0.187		
O charge	–0.371	–0.399	–0.407	–0.417	–0.536	–0.548

[a] Donor-acceptor orbital interactions in kcal/mol.

used to support the considerable preference for formation of HOE intermediates.

All chemicals were purchased from either Fluka or Merck. Solvents were purified and dried by standard procedures, and stored over 3 Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). Melting points were measured using a Büchi-510 apparatus in open capillaries and are uncorrected. IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. ^{1}H and ^{13}C NMR Spectra were obtained using a Bruker Avance-DPX-250 spectrometer operating at 250/62.5 MHz, respectively (δ in ppm, *J* in Hz). GC/MS were performed on a Shimadzu GC/MS-QP 1000-EX apparatus (*m*/*z*; rel%). Elemental analyses were performed on a Perkin–Elmer 240-B microanalyzer.

Three-Component Synthesis of *N*-Heterocycle Methyl-*O*-oxime Ethers 3a–r; General Procedure

In a double-necked round-bottomed flask (100 mL) equipped with a condenser was added a mixture consisting of oxime (0.01 mol), nitrogen heterocycle (0.01 mol), methylene iodide (2.67 g, 0.01 mol), Et_3N (1.01 g, 0.01 mol), and K_2CO_3 (1.38 g, 0.01 mol) in anhyd MeCN (40 mL). The mixture was heated at reflux until TLC (eluent: see R_f for products listed below) indicated no further improvement in the conversion (Table 4). The solvent was evaporated under vacuum and the remaining foam was dissolved in $CHCl_3$ (100 mL) and subsequently washed with H_2O (2 × 100 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography on silica gel eluting with the solvents described below for R_f.

Benzophenone *O*-(1*H*-Imidazol-1-yl) Methyl Oxime (3a)

Yellow crystals; mp 104.9 °C; R_f = 0.68 (EtOAc–*n*-hexane, 5:1).

IR (KBr): 3047, 2939, 1691, 1481 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.36 (s, 2 H, OCH_2N), 6.76–7.16 (m, 12 H, aryl, H-4 and H-5, imidazole), 7.36 (s, 1 H, H-2, imidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 77.69, 119.22, 127.99, 128.13, 128.58, 128.83, 129.08, 129.67, 129.98, 132.63, 135.37, 137.84, 159.68.

MS: *m*/*z* (%) = 277.12 (21.3).

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.71; H, 5.49; N, 15.13.

Benzophenone *O*-(1*H*-Benzo[*d*]imidazol-1-yl) Methyl Oxime (3b)

Bright brown crystals; mp 116.4 °C; R_f = 0.60 (EtOAc–*n*-hexane, 3:1).

IR (KBr): 3025, 2954, 1695, 1434 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.84 (s, 2 H, OCH_2N), 7.03–7.82 (m, 14 H, aryl), 8.01 (s, 1 H, H-2, benzimidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 76.20, 110.59, 120.27, 122.69, 123.34, 128.06, 128.14, 128.31, 128.93, 129.11, 129.66, 130.01, 132.62, 133.58, 135.39, 144.01, 159.71.

MS: *m*/*z* (%) = 327.14 (25.9).

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.01; H, 5.29; N, 12.81.

Benzophenone *O*-(2-Methyl-4-nitro-1*H*-imidazol-1-yl) Methyl Oxime (3c)

Pale-yellow crystals; mp 135.5 °C; R_f = 0.90 (EtOAc–*n*-hexane, 2:1).

IR (KBr): 3021, 2928, 2848, 1648, 1530, 1494, 1334 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3), 5.72 (s, 2 H, OCH_2N), 7.09–7.38 (m, 10 H, aryl), 7.82 (s, 1 H, H-5, imidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.25, 77.78, 120.12, 128.08, 128.30, 128.46, 128.68, 128.74, 129.44, 130.46, 132.25, 134.81, 145.59, 161.33.

MS: *m*/*z* (%) = 336.12 (43.8).

Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.33; H, 4.81; N, 16.61.

7-Benzhydrylideneaminooxymethyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione (3d)

Pale-yellow crystals; mp 154.4 °C; R_f = 0.71 (EtOAc–*n*-hexane, 2:1).

IR (KBr): 3085, 2939, 1720, 1704, 1643, 1434 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.33 (s, 3 H, N1-CH_3), 3.53 (s, 3 H, N3-CH_3), 6.16 (s, 2 H, OCH_2N), 7.15–7.35 (m, 10 H, aryl), 7.95 (s, 1 H, H-8, theophylline).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.84, 29.72, 60.24, 106.26, 128.00, 128.11, 128.21, 129.08, 129.26, 129.99, 132.09, 135.38, 142.28, 148.75, 151.57, 154.85, 170.97.

MS: *m*/*z* (%) = 389.15 (34.6).

Anal. Calcd for $C_{21}H_{19}N_5O_3$: C, 64.77; H, 4.92; N, 17.98. Found: C, 64.84; H, 4.98; N, 17.91.

1,3-Diphenylpropan-2-one *O*-(2-Methyl-4-nitro-1*H*-imidazol-1-yl) Methyl Oxime (3e)

Pale-yellow crystals; mp 59.0 °C R_f = 0.53 (EtOAc–*n*-hexane, 1:1).

IR (KBr): 3050, 2968, 2848, 1693, 1525, 1453, 1339 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 3.40 (s, 2 H, PhCH_2), 3.54 (s, 2 H, PhCH_2), 5.74 (s, 2 H, OCH_2N), 6.93–7.06 (m, 4 H, aryl), 7.13–7.36 (m, 6 H, aryl), 7.77 (s, 1 H, H-5, imidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.07, 33.83, 39.86, 77.31, 120.23, 126.87, 127.08, 128.59, 128.68, 128.76, 128.90, 129.09, 135.34, 135.43, 145.49, 162.72.

MS: *m*/*z* (%) = 364.15 (37.1).

Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.87; H, 5.59; N, 15.34.

1,3-Diphenylpropan-2-one *O*-(1*H*-Benzo[*d*]imidazol-1-yl) Methyl Oxime (3f)

Brown crystals; mp 57.8 °C; R_f = 0.72 (EtOAc–*n*-hexane, 4:1).

IR (KBr): 3100, 2952, 2847, 1686, 1470 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.26 (s, 2 H, PhCH_2), 3.41 (s, 2 H, PhCH_2), 5.90 (s, 2 H, OCH_2N), 6.79–7.81 (m, 14 H, aryl), 7.97 (s, 1 H, H-2, benzimidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 33.45, 39.52, 75.87, 110.62, 120.21, 122.68, 123.40, 126.60, 126.87, 128.58, 128.84, 129.11, 129.35, 129.88, 133.51, 135.41, 135.97, 143.82, 161.27.

MS: *m*/*z* (%) = 355.17 (29.5).

Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.63; H, 6.01; N, 11.70.

7-(1-Benzyl-2-phenylethylideneaminooxymethyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (3g)

Pale-yellow crystals; mp 125.6 °C; R_f = 0.70 (EtOAc–*n*-hexane, 2:1).

IR (KBr): 3065, 2931, 2871, 1718, 1705, 1691, 1446 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.39 (s, 4 H, PhCH_2), 3.51 (s, 3 H, N1-CH_3), 3.62 (s, 3 H, N3-CH_3), 6.18 (s, 2 H, OCH_2N), 6.95–7.31 (m, 10 H, aryl), 7.77 (s, 1 H, H-8, theophylline).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.96, 29.85, 33.72, 39.83, 76.85, 106.19, 126.49, 126.96, 128.40, 128.62, 128.83, 129.11, 135.64, 135.77, 142.20, 148.91, 151.66, 154.98, 162.29.

MS: *m*/*z* (%) = 417.18 (37.3).

Anal. Calcd for $C_{23}H_{23}N_5O_3$: C, 66.17; H, 5.55; N, 16.78. Found: C, 66.19; H, 5.59; N, 16.71.

(*E*)-Acetophenone *O*-(1*H*-Benzo[*d*]imidazol-1-yl) Methyl Oxime (3h)

Pale-yellow crystals; mp 134.2 °C; R_f = 0.58 (EtOAc–*n*-hexane, 3:1).

IR (KBr): 3100, 2975, 2845, 1693, 1459 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, CH_3), 5.89 (s, 2 H, OCH_2N), 7.21–7.79 (m, 9 H, aryl), 8.05 (s, 1 H, H-2, benzimidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.84, 75.99, 110.42, 120.24, 122.61, 123.32, 126.48, 128.38, 129.30, 129.62, 133.55, 135.47, 143.81, 157.29.

MS: *m*/*z* (%) = 265.12 (40.7).

Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.33; H, 5.81; N, 15.71.

(*E*)-1,3-Dimethyl-7-(1-phenylethylideneaminooxymethyl)-3,7-dihydropurine-2,6-dione (3i)

Pale-yellow crystals; mp 164.8 °C; R_f = 0.68 (EtOAc–*n*-hexane, 2:1).

IR (KBr): 3070, 2952, 2865, 1720, 1708, 1686, 1465 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, CH_3), 3.42 (s, 3 H, N1-CH_3), 3.55 (s, 3 H, N3-CH_3), 6.23 (s, 2 H, OCH_2N), 7.33–7.37 (m, 3 H, aryl), 7.53–7.57 (m, 2 H, aryl), 7.90 (s, 1 H, H-8, theophylline).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.25, 27.97, 29.2, 76.97, 106.21, 126.55, 128.45, 129.82, 135.39, 142.44, 148.94, 151.61, 155.09, 158.18.

MS: *m*/*z* (%) = 327.13 (28.4).

Anal. Calcd for $C_{16}H_{17}N_5O_3$: C, 58.71; H, 5.23; N, 21.39. Found: C, 58.75; H, 5.31; N, 21.48.

(*E*)-4-Phenylbutan-2-one-*O*-(1*H*-benzo[*d*]imidazol-1-yl) Methyl Oxime (3j)

Bright-brown foam; R_f = 0.67 (EtOAc–*n*-hexane, 4:1).

IR (film): 3057, 2930, 2848, 1695, 1464 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.53 (s, 3 H, CH_3), 2.19 (t, *J* = 7.2 Hz, 2 H, CH_2CN), 2.58 (t, *J* = 7.2 Hz, 2 H, PhCH_2), 5.70 (s, 2 H, OCH_2N), 6.88–7.64 (m, 9 H, aryl), 7.80 (s, 1 H, H-2, benzimidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.84, 32.13, 37.53, 75.76, 110.46, 120.20, 122.55, 123.25, 126.14, 128.09, 128.24, 128.44, 133.57, 140.87, 143.70, 159.94.

MS: *m*/*z* (%) = 293.15 (43.0).

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.64; H, 6.49; N, 14.24.

(*E*)-1,3-Dimethyl-7-(1-methyl-3-phenylpropylideneamino-oxymethyl)-3,7-dihydropurine-2,6-dione (3k)

Pale-yellow crystals; mp 112.1 °C; R_f = 0.71 (EtOAc–*n*-hexane, 2:1).

IR (KBr): 3100, 2948, 2860, 1723, 1705, 1692, 1458 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, CH_3), 2.45 (t, *J* = 7.3 Hz, 2 H, CH_2CN), 2.79 (t, *J* = 7.3 Hz, 2 H, PhCH_2), 3.42 (s, 3 H, N1-CH_3), 3.61 (s, 3 H, N3-CH_3), 6.07 (s, 2 H, OCH_2N), 7.11–7.29 (m, 5 H, aryl), 7.69 (s, 1 H, H-8, theophylline).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.01, 27.96, 29.82, 32.08, 37.42, 76.67, 106.16, 126.15, 128.17, 128.41, 140.68, 142.27, 148.84, 151.66, 155.07, 160.61.

MS: *m*/*z* (%) = 355.16 (27.4).

Anal. Calcd for $C_{18}H_{21}N_5O_3$: C, 60.83; H, 5.96; N, 19.71. Found: C, 60.79; H, 5.90; N, 19.63.

Cyclohexanone *O*-(1*H*-Benzo[*d*]imidazol-1-yl) Methyl Oxime (3l)

Pale-yellow crystals; mp 114.7 °C; R_f = 0.64 (EtOAc–*n*-hexane, 4:1).

IR (KBr): 3065, 2954, 2849, 1694, 1473 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33–1.40 (m, 6 H, 3 CH_2), 1.94–2.03 (m, 4 H, 2 CH_2), 5.84 (s, 2 H, OCH_2N), 6.17–7.73 (m, 4 H, aryl), 8.09 (s, 1 H, H-2, benzimidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.13, 21.32, 25.52, 26.73, 31.94, 75.76, 110.52, 119.75, 122.73, 123.39, 133.32, 143.61, 163.62, 174.61.

MS: *m*/*z* (%) = 243.14 (45.2).

Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.17; H, 7.12; N, 17.20.

7-Cyclohexylideneaminooxymethyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione (3m)

Pale-yellow crystals; mp 130.9 °C; R_f = 0.64 (EtOAc–*n*-hexane, 2:1).

IR (KBr): 3085, 2939, 2877, 1720, 1706, 1698, 1434 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45–1.55 (m, 6 H, 3 CH_2), 2.04–2.09 (m, 4 H, 2 CH_2), 3.31 (s, 3 H, N1-CH_3), 3.52 (s, 3 H, N3-CH_3), 6.00 (s, 2 H, OCH_2N), 7.78 (s, 1 H, H-8, theophylline).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 24.59, 25.14, 25.53, 26.76, 27.83, 29.69, 31.88, 76.54, 106.06, 142.24, 148.73, 151.54, 154.94, 163.78.

MS: *m*/*z* (%) = 305.15 (36.8).

Anal. Calcd for $C_{14}H_{17}N_3O$: C, 55.07; H, 6.27; N, 22.94. Found: C, 55.10; H, 6.21; N, 22.86.

(*E*)-7-*sec*-Butylideneaminooxymethyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione (3n)

Pale-yellow crystals; mp 106.7 °C; R_f = 0.56 (EtOAc–*n*-hexane, 3:1).

IR (KBr): 3070, 2983, 2865, 1724, 1707, 1693, 1472 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.76 (q, *J* = 7.4 Hz, 2 H, CH_2Me), 2.06 (s, 1 H, CH_3), 3.31 (s, 3 H, N1-CH_3), 3.49 (s, 3 H, N3-CH_3), 6.02 (s, 2 H, OCH_2N), 7.82 (s, 1 H, H-8, theophylline).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 10.68, 19.26, 21.14, 28.97, 29.70, 76.53, 106.02, 142.46, 148.60, 151.52, 158.83, 162.35.

MS: *m*/*z* (%) = 279.13 (34.5).

Anal. Calcd for $C_{14}H_{17}N_3O$: C, 51.60; H, 6.14; N, 25.08. Found: C, 51.57; H, 6.23; N, 25.01.

Propan-2-one *O*-(2-Methyl-4-nitro-1*H*-imidazol-1-yl) Methyl Oxime (3o)

Pale-yellow crystals; mp 114.4 °C; R_f = 0.90 (EtOAc–*n*-hexane, 2:1).

IR (KBr): 3021, 2958, 2848, 1695, 1533, 1494, 1344 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.77 (s, 6 H, 2 CH_3), 2.43 (s, 3 H, CH_3), 5.61 (s, 2 H, OCH_2N), 7.77 (1 H, s, H-5, imidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.13, 15.78, 21.64, 77.13, 120.36, 145.39, 151.16, 159.02.

MS: *m*/*z* (%) = 212.09 (25.1).

Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.34; H, 5.79; N, 26.32.

Propan-2-one *O*-(1*H*-Benzo[*d*]imidazol-1-yl) Methyl Oxime (3p)

Pale-yellow crystals; mp 90.7 °C; R_f = 0.48 (EtOAc–*n*-hexane, 1:3).

IR (KBr): 3073, 2934, 2870, 1687, 1468 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.73 (s, 6 H, 2 CH_3), 5.53 (s, 2 H, OCH_2N), 6.91–7.50 (m, 4 H, aryl), 7.70 (s, 1 H, H-2, benzimidazole).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.52, 21.15, 75.51, 110.31, 119.98, 121.93, 122.33, 123.07, 133.41, 143.62, 157.57.

MS: *m*/*z* (%) = 203.11 (40.5).

Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.09; H, 6.51; N, 20.56.

Propan-2-one *O*-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl) Methyl Oxime (3q)

White crystals; mp 157.6 °C; R_f = 0.87 (EtOAc–*n*-hexane, 1:1).

IR (KBr): 3080, 2962, 2875, 1697, 1454 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.68 (s, 6 H, 2 CH_3), 6.32 (s, 2 H, OCH_2N), 7.26–7.97 (m, 4 H, aryl).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.73, 23.89, 78.33, 110.79, 118.63, 119.66, 124.06, 127.57, 133.19, 158.09.

MS: *m*/*z* (%) = 204.10 (22.9).

Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.75; H, 5.98; N, 27.37.

7-Isopropylideneaminooxymethyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione (3r)

White crystals; mp 154.4 °C; R_f = 0.55 (EtOAc–*n*-hexane, 1:2).

IR (KBr): 3085, 2958, 2863, 1720, 1704, 1694, 1482 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.75 (s, 6 H, 2 CH_3), 3.31 (s, 3 H, N1-CH_3), 3.49 (s, 3 H, N3-CH_3), 6.01 (s, 2 H, OCH_2N), 7.77 (s, 1 H, H-8, theophylline).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 15.91, 21.65, 27.83, 29.68, 76.52, 106.03, 142.27, 148.78, 151.53, 154.92, 158.43.

MS: *m*/*z* (%) = 265.12 (32.6).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.72; H, 5.76; N, 26.37.

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