SUPPLEMANTARY INFORMATIONS

An experimental and Theoretical Study of Reaction Mechanism between Nitriles and Hydroxylamine

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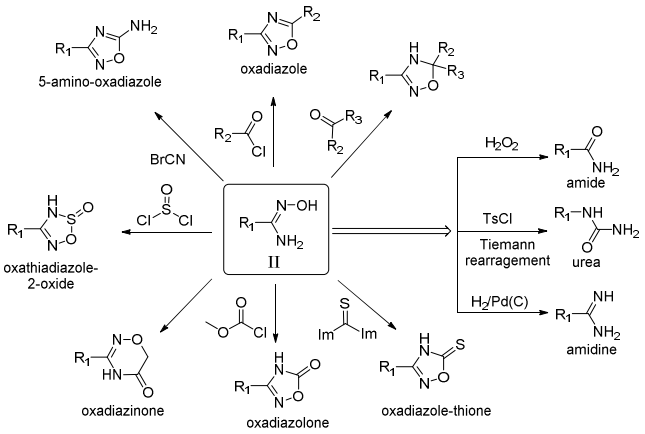
1. Experimental HPLC methods

All the reactions were tracked using appropriate HPLC methods on Agilent 1100 equipment, column temperature was 30 °C, the flow rate was 1.0 mL/min in each of the five methods below.

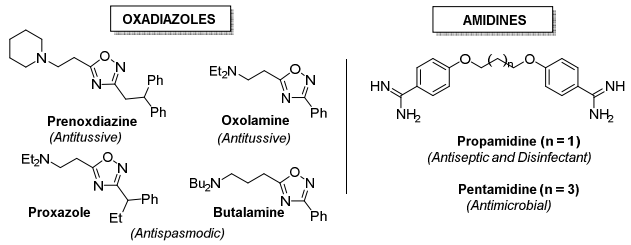
Table S1. HPLC methods, developed to follow the reactions**.**

Method No	Column	Buffer	Eluent	Gradient
1	Waters Symmetric C18 4.6x150mm, 5 µm	pH = 2.5 0.01M KH_2PO_4/H_3PO_4	ACN	10% → 90% ACN, 5 min 90% ACN, 1 min 90% → 10% ACN, 0.1 min 10% ACN, 3.9 min
2				30% → 90% ACN, 5 min 90% ACN, 1 min 90% → 30% ACN, 0.1 min 30% ACN, 3.9 min
3		-	H_2O/ACN	95% ACN, 4 min 95% → 90% ACN, 5 min 90% → 30% ACN, 3 min 30% → 95% ACN, 0.5 min 95% ACN, 4.5 min 3% ACN, 2 min
4	Waters Symmetric C18 4.6x250mm, 5 µm	pH = 2.5 0.01M KH_2PO_4/H_3PO_4	ACN	3% → 80% ACN, 3 min 80% ACN, 1 min 80% → 3% ACN, 0.1 min 3% ACN, 3.9 min
5	LiChrospher 60 RP-select B, 5 µm	pH = 8 0.01M K_2HPO_4/H_3PO_4	ACN	10% → 80% ACN, 5 min 80% ACN, 1 min 80% → 10% ACN, 0.1 min 10% ACN, 3.9 min

2. Application of amidoximes



Scheme S1. General reaction pathways starting from amidoximes (**II**) toward heterocycles and selected important functional groups



Scheme S2. Selected 1,2,4-oxadiazoles and amidines units introduced into drugs for human therapy

3. Experimental results

Table S2. 30 min reaction time in EtOH or [BMIM][OAc] with 1 eqv. or 2. eqv. Et_3N at 50 °C

Entry	BN		EtOH				[BMIM][OAc]			
			1. eqv. Et_3N		2. eqv. Et_3N		1. eqv. Et_3N		2. eqv. Et_3N	
			2a–m	**3a–m**	**2a–m**	**3a–m**	**2a–m**	**3a–m**	**2a–m**	**3a–m**
1	BN	**1a**	76	1	74	3	98	1	97	1
2	4-Cl	**1b**	90	3	90	5	97	3	97	2
3	4-F	**1c**	85	1	84	3	98	1	98	1
4	4-NO_2	**1d**	99	1	97	3	100	0	100	0
5	4-MeO	**1e**	45	2	40	4	83	2	83	3
6	4-Me	**1f**	46	1	40	2	78	2	87	2
7	2-Cl	**1g**	20	3	13	2	59	2	61	1
8	2-NO_2	**1h**	51	17	41	23	99	1	98	1
9	2-MeO	**1i**	9	1	7	1	38	1	40	1
10	2-MeO[a]	**1i**	40	2	–	–	59	5	–	–
11	2-Me	**1j**	10	1	8	1	58	1	63	1
12	2-Me[a]	**1j**	33	5	–	–	86	2	–	–
13	4-Py	**1k**	100	0	99	1	100	0	100	0
14	2-Py	**1l**	100	0	92	8	100	0	99	1
15	2,6-Me	**1m**	16	0	11	0	42	0	42	0

[a]in EtOH 20h/ in [BMIM][OAc] 10h

Table S3. Variation of the different reaction conditions in molecular solvent (EtOH and/or water) and the results obtained for the mechanistic study.

Entry	Reaction condition			Results	
	Reactant	Reagent / Base	Solvent / Temp	BAO	BA
1	BN	$NH_2OH.HCl/TEA$[a]	EtOH / 80 °C	95%	5%
2		$NH_2OH.H_2O$	EtOH / 80 °C	80%	20%
3		–	H_2O / 50 °C	NO	NO
4		–	EtOH / 50 °C	NO	NO
5		Na_2CO_3	H_2O / 50 °C	NO	NO
6		Na_2CO_3	EtOH / 50 °C	NO	NO
7		Na_2CO_3	EtOH+H_2O / 50 °C	NO	NO
8		$NH_2OH.HCl/NaH$	ACN / 45 °C	NO	100%
9	BAO	–	EtOH / 50 °C	–	NO
10		Na_2CO_3	EtOH / 50 °C	–	NO
11		–	EtOH+H_2O / 50 °C	–	NO
12		Na_2CO_3	EtOH+H_2O / 50 °C	–	NO
13		$NH_2OH.HCl/TEA$	EtOH / 50 °C	–	NO

[a]Normal preparation of BAO

Table S4A. Row HPLC integrals (A) of the HPLC peaks belong to the reaction components in Me-THF in the function of time.

Time (s)	A(BAO)	A(BA)	A(BN)	A(toluene)
0	0	0	2246.2	553.9
135	0	0	2118.3	520.4
420	0	0	1990	470.5
550	10.5	7.5	2849.9	681.9
900	12.5	5	2385.5	580.2
1200	15.3	5	2406.1	568.1
2100	37.3	13.7	2581.4	628.3
3000	44.1	11.4	2281.4	528.6
5400	90.6	21.4	1968.1	460.1
9000	1317.3	213	2317.5	671.3
14400	1368.1	90.1	1908.9	554.3
57600	3252.3	375.9	826.7	623

Table S4B. **Relative concentrations** of the reaction components in Me-THF in the function of time. Relative concentration of X = A(X)/ A(toluene).

Time (s)	BAO	BA	BN
0	0	0	0.56711
135	0	0	0.569246
420	0	0	0.591485
550	0.002153	0.001538	0.584466
900	0.003013	0.001205	0.574979
1200	0.003766	0.001231	0.592296
2100	0.008302	0.003049	0.574564
3000	0.011667	0.003016	0.603565
5400	0.027538	0.006504	0.598198
9000	0.274421	0.044372	0.482784
14400	0.345162	0.022732	0.481602
57600	0.73005	0.084379	0.185571

Table S5A. Row HPLC integrals (A) of the HPLC peaks belong to the reaction components in n-PrOH in the function of time.

Time (s)	A(BAO)	A(BA)	A(BN)	A(toluene)
0	59.2	3.3	1924	493.9
420	453	34.5	1695.8	472.9
550	495.8	20.7	390	145.2
900	2431.7	109	941.8	504.4
1200	3125.3	116.8	1041	624
2100	2973	104.5	506.8	449.3
3000	3806.3	128.5	231.9	466.9
5400	4773.9	158.3	92.8	538
9000	4801.1	163.3	22.2	516.7
14400	4011.3	135.3	15	434.9
57600	5081.3	180	33	480.5

Table S5B. Relative concentrations of the reaction components in n-PrOH in the function of time. Relative concentration of X = A(X)/ A(toluene).

Time (s)	BAO	BA	BN
0	0.010878	0.000606	0.35355
420	0.086939	0.006621	0.325454
550	0.309902	0.012939	0.243771
900	0.437542	0.019613	0.16946
1200	0.454561	0.016988	0.151409
2100	0.600542	0.021109	0.102373
3000	0.739885	0.024978	0.045078
5400	0.805334	0.026704	0.015655
9000	0.84331	0.028684	0.003899
14400	0.862201	0.028235	0.00313
57600	0.959768	0.033999	0.006233

Table S6A. Row HPLC integrals (A) of the HPLC peaks belong to the reaction components in i-PrOH in the function of time.

Time (s)	A(BAO)	A(BA)	A(BN)	A(toluene)
0	26.1	0.0	1948.3	496.0
420	178.7	10.7	1864.5	487.2
550	974.2	54.3	2020.7	623.1
900	1269.4	77.4	1844.4	618.0
1200	1380.9	76.0	1654.2	574.2
2100	2074.5	110.3	1243	542.4
3000	3384.0	152.9	768.6	547.4
5400	4552.1	176.2	134.9	527.3
9000	4676.1	173.6	24.3	517.2
14400	4686.4	170.1	0.0	540.6
57600	3948.4	148.1	0.0	396.9

Table S6B. Relative concentrations of the reaction components in i-PrOH in the function of time. Relative concentration of X = A(X)/ A(toluene).

Time (s)	BAO	BA	BN
0	0.005098	0	0.380577
420	0.035537	0.002128	0.370786
550	0.151481	0.008443	0.314204
900	0.199011	0.012134	0.289158
1200	0.233006	0.012824	0.279121
2100	0.370563	0.019703	0.222034
3000	0.598954	0.027063	0.136039
5400	0.813856	0.032375	0.024787
9000	0.875978	0.032521	0.004552
14400	0.839907	0.030486	0
57600	0.963847	0.036153	0

Table S7A. Row HPLC integrals of the HPLC peaks (A) belong to the reaction components in t-BuOH in the function of time.

Time (s)	A(BAO)	A(BA)	A(BN)	A(toluene)
0	0	0	831.4	248
420	72.7	10.7	1548.7	440
550	278.6	34.2	1561	470.4
900	486.7	53.2	2264.5	685.7
1200	510.3	53.3	1794.4	567.6
2100	818	84.3	1492.4	517.3
3000	1944.6	172	1400.9	659.2
5400	3619	292.9	746.7	698.6
9000	4327.5	310.5	238.4	622.7
14400	3981.4	263.1	35.8	509.5
57600	4554	302	0	531.5

Table S7B. Relative concentrations of the reaction components in t-BuOH in the function of time. Relative concentration of X = A(X)/ A(toluene).

Time (s)	BAO	BA	BN
0	0	0	0.36693
420	0.018084	0.002662	0.385247
550	0.064824	0.007958	0.363212
900	0.077688	0.008492	0.361462
1200	0.098403	0.010278	0.34602
2100	0.173075	0.017837	0.315767
3000	0.322877	0.028559	0.232603
5400	0.567002	0.04589	0.116988
9000	0.760646	0.054577	0.041904
14400	0.855296	0.05652	0.007691
57600	0.937809	0.062191	0

Table S8A. Row HPLC integrals of the HPLC peaks (A) belong to the reaction components in [BMIM][OAc] in the function of time.

Time (s)	A(BAO)	A(BA)	A(BN)	A(toluene)
135	739.1	50.2	623.1	188.2
550	1192.9	70.5	377.6	262.9
900	947.6	52.2	284.2	312.5
1200	2031.1	110.2	181.3	254.3
2100	2403.6	131.4	88.1	243.9
3000	2309.1	125.7	48.7	157.4
5400	1495.6	85.7	0	96
9000	1784.3	108.2	0	109.5
57600	10745.7	388.4	0	643.7

Table S8B. Relative concentrations of the reaction components in [BMIM][OAc] in the function of time. Relative concentration of X = A(X)/ A(toluene).

Time (s)	BAO	BA	BN
135	0.227045	0.015421	0.191411
550	0.262326	0.015503	0.083037
900	0.175309	0.009657	0.052578
1200	0.461757	0.025053	0.041217
2100	0.569743	0.031147	0.020883
3000	0.848138	0.04617	0.017888
5400	0.900684	0.05161	0
9000	0.942068	0.057127	0
57600	0.965116	0.034884	0

4. Row computational data

Table S9A. Row data of small compounds, computed at the B3LYP/6-31G(d,p) level of theory in MeCN. The E, ZPE, U, H and G values are given in Hartree, while S is given in J/mol/K.

	E	ZPE	U	H	G	S	Svib
H2	-1.17853933	-1.168363	-1.166003	-1.165058	-1.179850	31.132	0.000
BN	-324.5073629	-324.407997	-324.402	-324.401	-324.438	78.516	10.895
TMA	-174.4881329	-174.36768	-174.362	-174.361	-174.395	70.776	8.347
TMA+H+	-174.9525533	-174.815552	-174.81	-174.809	-174.843	71.543	8.875
NH2OH	-131.7217604	-131.681722	-131.678	-131.677	-131.704	56.426	1.482
NH2O–	-131.1688842	-131.143673	-131.141	-131.14	-131.166	54.599	0.245
NH–OH	-131.1490263	-131.125189	-131.122	-131.121	-131.147	55.821	1.299
NH3+OH	-132.1600825	-132.104625	-132.101	-132.1	-132.127	56.777	1.348
NH2OH2+	-132.1170121	-132.06376	-132.06	-132.059	-132.087	57.364	1.833
NH3+O–	-131.6916621	-131.650645	-131.648	-131.647	-131.672	52.899	0.221
NH2ONH2	-187.0279304	-186.971203	-186.967	-186.966	-186.997	64.527	5.137
NH2NHOH	-187.0563022	-186.998655	-186.995	-186.994	-187.024	62.988	3.52
MeOH	-115.7286955	-115.677374	-115.674	-115.673	-115.7	56.846	1.52
MeO-	-115.1854805	-115.149921	-115.147	-115.146	-115.171	52.697	0.151
MeOH2+	-116.1362709	-116.071497	-116.068	-116.067	-116.095	58.532	2.629
BA	-400.975869	-400.848203	-400.841	-400.84	-400.881	86.092	17.099
BAO/1	-456.2617832	-456.118395	-456.109	-456.108	-456.152	92.528	22.371
BAO/2	-456.2475815	-456.103319	-456.095	-456.094	-456.137	91.708	21.533
BAO/3	-456.248058	-456.104184	-456.096	-456.095	-456.138	90.884	20.731
BCO	-456.2495535	-456.105356	-456.096	-456.096	-456.14	94.084	23.947

Table S9B. Row data of compounds**,** computed at the B3LYP/6-31G(d,p) level of theory in MeCN. The E, ZPE, U, H and G values are given in Hartree, while S is given in J/mol/K.

	E	ZPE	U	H	G	S	Svib
7	-456.2361763	-456.095389	-456.084	-456.083	-456.135	107.845	36.941
TS(10->9)	-456.2050313	-456.063637	-456.055	-456.054	-456.098	92.993	22.785
11	**-921.442387**	**-920.98679**	**-920.958**	**-920.957**	**-921.057**	**211.056**	**132.478**
TS(11->12)	-921.4088507	-920.957996	-920.931	-920.93	-921.018	186.416	109.011
12	-921.4446698	-920.987128	-920.959	-920.958	-921.051	195.563	117.871
TS(11->13)	-921.4159063	-920.96298	-920.935	-920.934	-921.024	189.472	111.766
13	-921.4373343	-920.979762	-920.952	-920.951	-921.042	192.516	114.902
TS(12->14)	-920.93188	-920.93188	-920.905	-920.904	-920.992	183.755	106.308
14	-921.4347176	-920.977029	-920.95	-920.949	-921.039	188.795	111.16
TS(14->15)	-921.4136002	-920.962776	-920.936	-920.935	-921.024	188.176	110.458
15	-921.4454684	-920.990682	-920.963	-920.962	-921.053	192.064	114.265
TS(15->16)	-819.4264589	-819.138164	-819.118	-819.117	-819.19	153.238	77.395
16	-819.5020913	-819.207498	-819.186	-819.185	-819.263	163.223	87.298
TS(15->17)	-819.4397821	-819.147099	-819.127	-819.126	-819.2	155.839	79.928
17	-819.5233124	-819.230629	-819.21	-819.209	-819.283	155.7555	79.84447
18	-913.9719652	-913.717595	-913.695	-913.694	-913.777	174.991	97.634
TS(18->19)	-913.9571375	-913.702397	-913.682	-913.681	-913.757	160.558	83.709
19	-913.9810301	-913.724497	-913.704	-913.703	-913.78	162.804	85.67
TS(18->20)	-913.9580876	-913.704291	-913.684	-913.683	-913.759	159.686	82.962
20	-913.975928	-913.719201	-913.698	-913.697	-913.776	165.625	88.97
21	-587.9774045	-587.790285	-587.777	-587.776	-587.832	116.475	43.832
TS(21->22)	-587.910455	-587.725865	-587.714	-587.713	-587.766	112.288	39.664
22	-587.9298148	-587.744731	-587.732	-587.731	-587.785	114.301	41.7
TS(21->23)	-587.910455	-587.725865	-587.714	-587.713	-587.766	112.288	39.664
TS(24->25)	-587.8967833	-587.712997	-587.7	-587.699	-587.754	115.336	42.769
25	-587.9879333	-587.803572	-587.79	-587.789	-587.846	118.936	46.204
27	-587.8967833	-587.712997	-587.7	-587.699	-587.754	115.336	42.769
TS(27->28)	-587.9879333	-587.803572	-587.79	-587.789	-587.846	118.936	46.204
28	-587.9878678	-587.801988	-587.789	-587.788	-587.844	118.243	45.598

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