

Cycloaddition reactions of nitrosoalkenes, azoalkenes and nitrile oxides mediated by hydrotalcite

Américo Lemos* and João P. Lourenço*

CIQA, Departamento de Química e Farmácia, Faculdade de Ciências e Tecnologia,
Universidade do Algarve, Campus de Gambelas, 8005-139, Faro, Portugal
E-mail: alemos@ualg.pt, jlouren@ualg.pt

Dedicated to Professor António M. d'A Rocha Gonsalves
on the occasion of his 70th anniversary

DOI: <http://dx.doi.org/10.3998/ark.5550190.0011.515>

Abstract

Mg:Al 3:1 hydrotalcite (Ht), used in catalytic quantities, promotes the generation of nitrosoalkenes, azoalkenes and nitrile oxides. These can be intercepted *in situ* by heterocycles and olefins in [4+2] and [3+2] cycloaddition reactions, producing dihydro-1,2-oxazines, tetrahydropyridazines and isoxazolines. The regeneration and reuse of Ht without loss of activity and the absence of organic solvent are the main advantages of this methodology.

Keywords: Nitrosoalkene, azoalkene, nitrile oxide, hydrotalcite, cycloaddition

Introduction

The development of solid basic materials that can efficiently catalyse chemical reactions such as alkylations, isomerisations, condensations, cycloadditions, etc. in relatively benign conditions has gained a strong incentive in recent years due to economic demands and environmental concerns. Among those materials, the oxides obtained by thermal treatments of hydrotalcites (Hts) have shown promising properties.¹

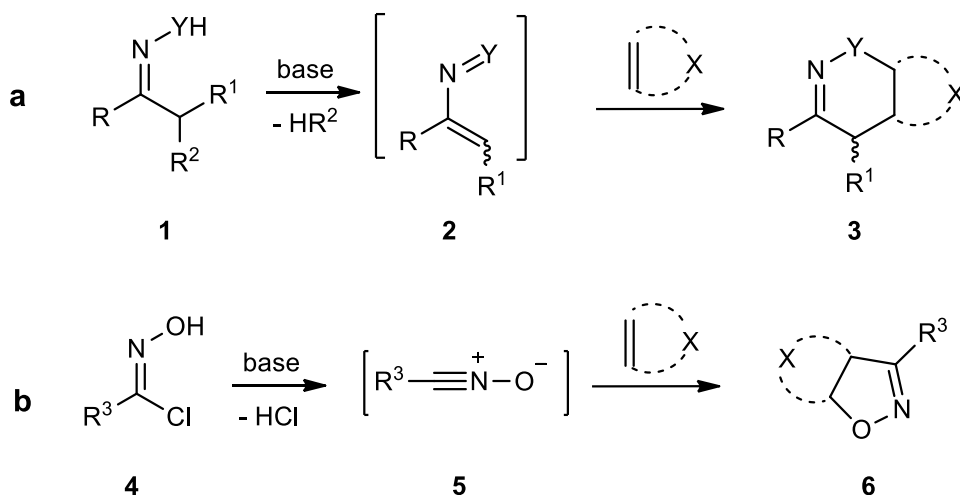
Hydrotalcite is an anionic clay belonging to the class of double layer hydroxides (DLHs) with the general formula $M_x^{2+}M_y^{3+}(\text{OH})_{2(x+y)}A_{y/n}^{-n}$ where M^{2+} and M^{3+} are a divalent and a trivalent metal ions, respectively, and A^{-n} is an intercalated anion. The most common metals are Mg and Al and in this case the structure is described as brucite-like ($\text{Mg}(\text{OH})_2$) sheets where various Mg^{2+} are isomorphously substituted by trivalent Al^{3+} . The positive charges of the structure are compensated by intercalated anions.

By controlled thermal decomposition, DLHs are converted in mixed oxides that show high

surface areas and strong basic properties.² The basic properties of calcined Mg-Al Hts are mainly associated with the Lewis basicity of the pairs $O^{2-} M^{2+}$. A controlled rehydration promotes a structural rearrangement, resulting in a Meixnerit-like compound, and changing the nature of the basic sites. The basic properties are now influenced by the presence of intercalated hydroxide anions.

The acid-base properties of these materials can be tuned, both in terms of the nature and strength of the basic sites, by choosing appropriate conditions for the synthesis and by post-synthesis treatments. Therefore, mixed oxides obtained from DLHs can be prepared with different acid-base properties that make them versatile catalysts for reactions that require different base catalysis.

Diels–Alder and 1,3-dipolar cycloaddition reactions are powerful methods for the construction of six- and five-membered rings in organic chemistry.³ Amongst these, cycloaddition reactions of nitrosoalkenes,⁴ azoalkenes⁵ and nitrile oxides⁶ are important tools for the synthesis of heterocyclic compounds containing nitrogen, such as 1,2-oxazines, pyridazines and isoxazolines.



$\text{R} = \text{CF}_3; \text{CHO}; \text{COR}^4; \text{CO}_2\text{R}^5; \text{C}_6\text{H}_5; 4\text{-NO}_2\text{C}_6\text{H}_4; \text{P}(\text{O})(\text{OR}^6)_3; \text{Me}$
 $\text{R}^1 = \text{H}; \text{Cl}; \text{P}(\text{O})(\text{OR}^6)_3; \text{P}(\text{O})\text{Ph}_3$
 $\text{R}^2 = \text{Br}; \text{Cl}$
 $\text{Y} = \text{O}; \text{N-CO}_2\text{R}^7; \text{N-C}_6\text{H}_4(\text{NO}_2)_2\text{-2,4}; \text{N-SO}_2\text{C}_6\text{H}_4\text{Me-4}$
 $\text{X} = \text{NR}^7; \text{O}; \text{CH}_2$
 $\text{R}^3 = \text{CO}_2\text{R}^5; \text{alkyl}; \text{phenyl}; \text{aryl}$

Scheme 1

The usual method for the generation of nitrosoalkenes and azoalkenes **2** is the base induced dehydrohalogenation of halogenated-oximes and hydrazones **1**. Similarly, nitrile oxides **5** are usually obtained by dehydrochlorination of hydroximidoyl chlorides **4** (Scheme 1). Since

nitrosoalkenes, azoalkenes and nitrile oxides are usually unstable and very reactive species, they must be generated in very low concentrations and trapped *in situ* by a dienophile or dipolarophile, usually present in a great excess, in order to minimize dimerizations and other side reactions. The low concentration of nitrosoalkenes, azoalkenes and nitrile oxides is commonly attained using a substantial volume of organic solvent and an inorganic base, the low solubility of which ensures a slow rate of dehydrohalogenation, or by a very slow addition of an organic base usually *via* syringe pump.

Recently we disclosed our preliminary results on the catalytic application of Mg:Al 3:1 hydrotalcite as mediating agent for [4+2] cycloaddition reactions of nitroso- and azo-alkenes by dehydrohalogenation of α -bromo oximes and hydrazones.⁷ Our efforts and attempts to broaden the scope into other halogenated oximes, hydrazones and hydroximidoyl chlorides as well as the generation of other 1,3-dipoles, are the subject of this work.

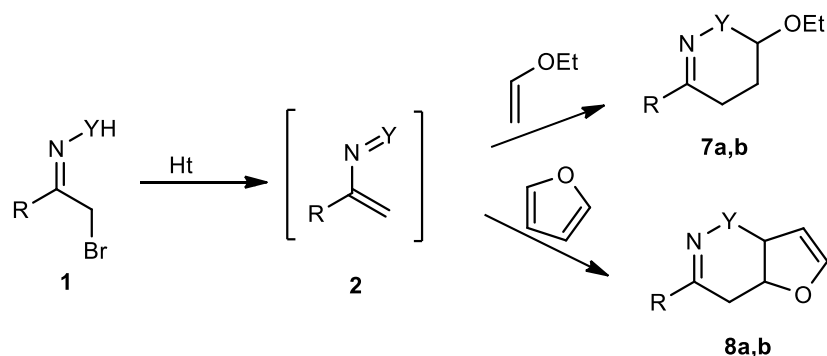
Results and Discussion

Reaction conditions

Initially, different ratios of Ht and oxime **1a** in common organic solvents with diverse polarities and volumes were explored in reactions with ethyl vinyl ether and furan, but with negative results (Table 1, entries 1-4). Under these conditions the starting materials were recovered unchanged. The presence of water soon appeared to be obligatory, presumably in order to rehydrate the Ht, since in all the reactions conducted in its absence no product could be detected or isolated.

The best results were obtained when the oxime or hydrazone was dissolved in the dienophile and 0.05 mL (or two drops) of water were added and, finally, the Ht introduced in a 10% mass ratio to the oxime or hydrazone (entries 11, 12).

Larger amounts of water and/or solvent gave rise to lower yields and very complicated mixtures of reaction products (entries 5, 6, 8, 9). Also, in control reactions performed in the absence of Ht (entry 13), or when Ht was replaced by sodium carbonate – maintaining the same reaction conditions (entry 14) – no reaction products were detected. We were also pleased to find that the Ht filtered from the reaction media, washed with water and acetone, dried and calcined (500 °C under a flux of dry air), could be used again without loss of activity (entries 15,16).

Table 1. Ht mediated cycloaddition reactions with furan and ethyl vinyl ether

Entry	R	Y	Ht / 1 ^a	Solvent (mL)	Product	Yield % ^b
1	CO ₂ Et	O	1/1	CH ₂ Cl ₂ (20)	7a	-
2	CO ₂ Et	O	1/1	CH ₂ Cl ₂ (20)	8a	-
3	CO ₂ Et	O	0.5/1	CH ₃ CN (10)	7a	-
4	CO ₂ Et	O	0.5/1	THF (10)	7a	-
5	CO ₂ Et	O	0.25/1	CH ₃ CN / 5% H ₂ O (10)	7a	9
6	CO ₂ Et	O	0.25/1	THF / 5% H ₂ O (10)	7a	18
7	CO ₂ Et	NCO ₂ CMe ₃	0.25/1	- ^c	8b	-
8	CO ₂ Et	NCO ₂ CMe ₃	0.25/1	H ₂ O (2)	7b	36
9	CO ₂ Et	O	0.1/1	H ₂ O (2)	7a	28
10	CO ₂ Et	O	0.1/1	H ₂ O (1.25)	7a	30
11	CO ₂ Et	O	0.1/1	H ₂ O (0.05)	7a	54 ^d
12	CO ₂ Et	NCO ₂ CMe ₃	0.1/1	H ₂ O (0.05)	7b	80 ^d
13	CO ₂ Et	O	- ^e	H ₂ O (0.05)	7a	-
14	CO ₂ Et	O	- ^f	H ₂ O (0.05)	7a	-
15	CO ₂ Et	O	0.1 ^g /1	H ₂ O (0.05)	7a	51 ^d
16	CO ₂ Et	NCO ₂ CMe ₃	0.1 ^g /1	H ₂ O (0.05)	7b	82 ^d

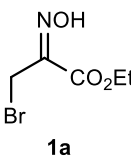

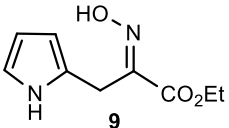
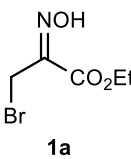
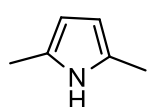
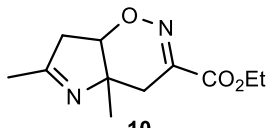
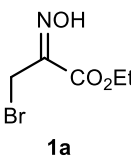
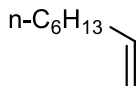
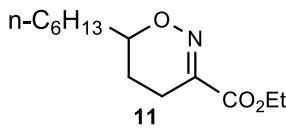
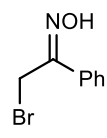

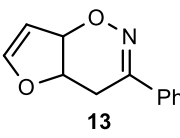
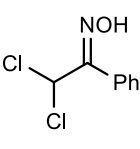

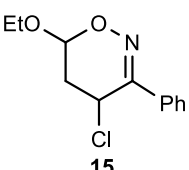
Reaction conditions: oxime or hydrazone (1mmol), dienophile (10 mmol), r.t., 16h.

^a Ht and oxime or hydrazone mass ratio. ^b isolated yields. ^c no solvent. ^d previously reported⁷. ^e no base. ^f Na₂CO₃ as base in 10% molar ratio of oxime. ^g regenerated and reused Ht

Scope and limitations of the Ht mediated generation of reactive species

Nitroso- and azo-alkenes. Having found reaction conditions for the Ht mediated cycloaddition reactions of α -bromooximes and α -bromohydrazones, we subsequently tried to evaluate the generality or scope of this methodology, by the application of this protocol to other α -halogenated oximes and hydrazones as well to other dienophiles or heterocycles.

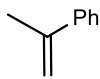
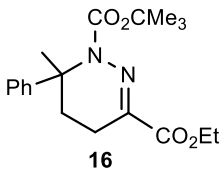
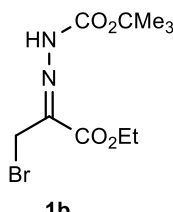

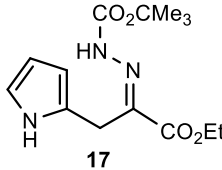
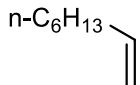
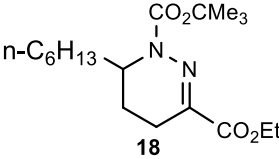

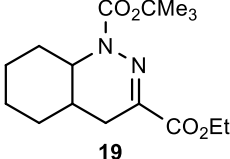
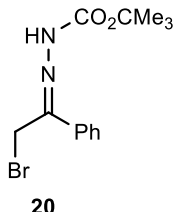

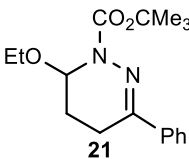

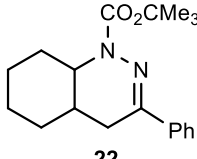
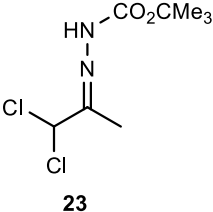

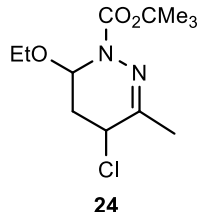
Table 2. Nitrosoalkene generation and cycloaddition reactions

Oxime	Alkene or Heterocycle	Product	Yield (%)	(%) ^{lit}
			45	61 ⁸
			24	70 ⁹
			-	3 ^{10, a}
			32	45 ¹¹
			41	79 ¹²

^a the oxime **1a** is not soluble in 1-octene.

The results outlined on Tables 2 and 3, show that the catalytic use of calcined Mg/Al 3:1 hydrotalcite constitutes an effective method for the generation of nitroso- and azo-alkenes from a variety of α -bromo- and α -dichloro-oximes and -hydrazones permitting their subsequent *in situ* interception by electron-rich alkenes and heterocycles affording adducts and cycloadducts in reasonable to good yields (the open chain oxime **9** and hydrazone **18** are postulated as resulting from the rearomatization of the primarily formed cycloadducts⁹).

Table 3. Azoalkene generation and cycloaddition reactions

Hydrazone	Alkene or Heterocycle	Product	Yield (%)	(%) ^{lit}
		 16	-	- ^a
 1b		 17	41	75 ¹³
		 18	-	- ^a
		 19	-	- ^a
 20		 21	54	-
		 22	-	- ^a
 23		 24	42	-

^a the hydrazone is not soluble in the dienophile.

The scope of this methodology appears to be limited to electron-deficient oximes and hydrazones that are soluble in the dienophile, and/or to electron-rich dienophiles that are able to solubilize the oxime or hydrazone, since no products could be detected when very low or no

solubility was observed, the starting materials being mainly recovered. The lack of solubility presumably prevents the easy access of the oxime and hydrazone to the Ht basic sites and consequently hinders the generation of the nitroso- or azo-alkene.

Nitrile oxide. Hydroxyimidoyl chlorides are commonly used as precursors of nitrile oxides. These are important transient species in the synthesis of 5-membered rings containing nitrogen and oxygen *via* 1,3-dipolar cycloadditions.^{3,6}

Table 4. Nitrile oxide generation and reactions

Dipolarophile	Product	Yield (%)	(%) ^{lit}
		31	29 ⁹
		64	78 ¹⁴
		49	58 ¹⁴ , 92 ¹⁵
		46	57 ⁹
		-	86 ¹⁶ ii

i - Ht 10% mass eq. hydroxyimidoyl chloride (2 mmol); dipolarophile (10 mmol); H₂O (0.05mL); r.t., 16h.

ii - hydroxyimidoyl chloride was insoluble in cyclohexene.

Cycloaddition of carboethoxyformonitrile oxide (CEFNO) with dipolarophiles is probably the most straightforward strategy towards isoxazolines carrying a carboxyl substituent. Thus, as a continuation of our studies on the catalytic application of Hts, we became interested in the

investigation, by an extension of the above methodology, of Ht mediated generation of CEFNO from ethyl chlorooximidoacetate **4**.

From the results of Table 4 it is possible to conclude that Ht used in catalytic quantities and without solvent is effective at the generation of CEFNO allowing its subsequent interception by a dipolarophile. The yields are comparable to those obtained by other methodologies, showing that this strategy is limited to dipolarophiles capable of solubilization of ethyl chlorooximidoacetate and the transient CEFN, as inferred from the reaction with cyclohexene. In the reactions under study, the furoxan usually formed by dimerization of nitrile oxide was only present to a small extent and no other regioisomers could be detected.

TosMIC deprotonation attempts. The methylene group of *p*-toluenesulfonylmethyl isocyanide (TosMIC) is highly activated by the two electron-withdrawing substituents. Likewise, deprotonation can be easily performed with various bases such K₂CO₃, NaOH and *n*-BuLi, amongst others.¹⁷ In this context, we were excited by the possibility of extending the above methodology to the deprotonation of TosMIC, but in all experiments, it was almost quantitatively recovered from the reaction media, suggesting that under the reaction conditions examined, the deprotonation did not occur, or if this did indeed happen, then the dipole so formed quickly reverted to the initial isocyanide and consequently interception by the dienophile/Michael acceptor could not take place.

Conclusions

In summary, we have disclosed a simple and effective method for the generation of electron-deficient nitrosoalkenes, azoalkenes and nitrile oxides *via* dehydrohalogenation of oximes and hydrazones, by the catalytic use of calcined Mg/Al 3:1 hydrotalcite and their subsequent interception by electron-rich alkenes and heterocycles, allowing the isolation of 5,6-dihydro-4*H*-1,2-oxazines, 1,4,5,6-tetrahydropyridazines and isoxazolines, the solubilisation of the 4π or the 2π reaction partner being a key factor in the process.

When compared with other commonly used strategies, this methodology has the advantages of requiring neither organic solvent nor inorganic base in large excess. The efficiency in [4+2] reactions is somewhat lower than in commonly used methods but comparable in [3+2] reactions and completely ineffective at the deprotonation of TosMIC. The absence of organic solvent as well the regeneration and reuse of Ht without loss of activity, may be valuable contributions to environmentally friendly, greener and economically valuable processes.

Experimental Section

General. ¹H NMR spectra and ¹³C NMR spectra (100.6 or 75.5 MHz) were recorded on a Bruker Avance III 400 (400 MHz) spectrometer or on a Bruker WM AMX (300 MHz), using TMS as

internal standard (chemical shifts (δ) in ppm, J in Hz). Multiplicities are recorded as broad peaks (br), broad singlets (bs), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). J values are in Hz and δ in ppm. Infrared spectra were recorded on a Bruker FT-IR Tensor 27 spectrophotometer. Samples were measured, if not otherwise stated, as thin films when oils or as KBr disks when solids, and the main bands are given in cm^{-1} . Melting points were measured on an EZ-Melt, Automated Melting Point Apparatus from Stanford Research Systems and are uncorrected. Powder XRD patterns were recorded on a Panalytical X'Pert diffractometer using $\text{CuK}\alpha$ radiation filtered by Ni and a X'Celerator detector. Nitrogen adsorption was measured at $-196\text{ }^\circ\text{C}$ using an ASAP 2010 Micromeritics apparatus. Prior to the measurements the samples were pre-treated under vacuum at $350\text{ }^\circ\text{C}$ for 3 h.

Synthesis of hydrotalcite with Mg/Al ratio of 3:1. Was performed following closely the method described in the literature.² A solution (100 ml) containing 0.1 mol of Na_2CO_3 and 0.3 mol of NaOH was mixed (at a rate of 1 mL/min) with 100 mL of a solution containing 0.111 mol of $\text{Mg}(\text{NO}_3)_2$ and 0.037 mol of $\text{Al}(\text{NO}_3)_3$ with stirring at room temperature. The gel was left for 18 h at $80\text{ }^\circ\text{C}$. The hydrotalcite was recovered by centrifugation, washed until pH 7 and dried at $80\text{ }^\circ\text{C}$ overnight. Before the catalytic tests, the hydrotalcite was activated at $450\text{ }^\circ\text{C}$ under a flux of dry nitrogen for 6 h.

XRD pattern of as-prepared hydrotalcite. Presented the characteristic peaks of clay minerals having layered structures and showed that well-crystallized hydrotalcite was formed.² The specific surface area of the calcined hydrotalcite was measured by N_2 adsorption at $-196\text{ }^\circ\text{C}$. The results obtained are similar to those found in the literature:² specific surface area (BET) of $253\text{ m}^2/\text{g}$, porous volume of $0,78\text{ cm}^3/\text{g}$ and average pore diameter ($4V_p/S_{\text{BET}}$) of 123 \AA .

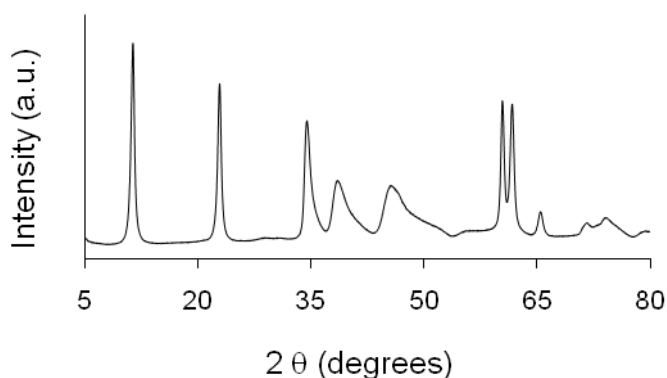


Figure 1. XRD pattern of as-prepared hydrotalcite.

Oximes 1a¹⁸, 12¹⁹, 14²⁰, hydrazone 1b¹³ and ethyl chlorooximidoacetate 4.¹⁶ Were synthesized according to literature procedures. Known isolated products were characterized by comparison of their physical, IR and NMR data with those reported in the literature.

2-Bromoacetophenone *t*-butoxycarbonyl hydrazone 20. To a stirred solution of 2-bromoacetophenone (2.70 g; 13.5 mmol) in diethyl ether (50 mL) was added *t*-butylcarbazate (1.97 g; 14.9 mmol) and the reaction mixture stirred at room temperature for 6 h. The white solid was then filtered off, washed with diethyl ether and dried, affording analytically pure hydrazone (2.86 g; 67%). m.p.(dec.): 124.6-126.4 °C; ν_{\max} : 3189, 2977, 1701, 1549, 1368, 1275, 1152, 1071; ^1H δ (400 MHz) 8.07 (s, 1H), 7.78-7.82 (2H, m), 7.38-7.43 (3H, m), 4.23 (2H, s), 1.58 (9H, s); ^{13}C δ (101 MHz) 152.8, 132.2, 130.4, 130.0, 128.9, 127.8, 126.3, 86.1, 35.3, 28.3, 19.0; HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{BrN}_2\text{NaO}_2$ 335.0371; found 335.0377.

1,1-Dichloroacetone *t*-butoxycarbonyl hydrazone 23. To a stirred solution of 1,1-dichloroacetone (1.4 mL; 14.3 mmol) in diethyl ether (60 mL) was added *t*-butylcarbazate (2.18 g; 16.5 mmol) and the reaction mixture stirred at room temperature for 16 h. The white solid was then filtered off, washed with diethyl ether and dried, affording analytically pure hydrazone (1.91 g; 55%). m.p.(dec.): 130.1-132.3 °C; ν_{\max} : 3197, 2983, 1708, 1537, 1253, 1144, 729; ^1H δ (400 MHz) 7.56 (1H, s), 6.40 (1H, s), 2.05 (3H, s), 1.53 (9H, s); ^{13}C δ (75 MHz) 156.8, 143.2, 80.7, 68.3, 28.4, 18.1; HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_8\text{H}_{14}\text{Cl}_2\text{N}_2\text{NaO}_2$ 263.0330; found 263.0326.

General procedure for cycloadditions

To the mixture of oxime (2 mmol), hydrazone (1 mol) or nitrile oxide (2 mmol) and dienophile or dipolarophile (10 or 20 mmol), was added water (0.05 mL) and Ht (10% in weight). After stirring for 6 to 16 h (TLC monitoring), the Ht was filtered off. Dry-flash chromatography of the filtrate (increasing polarity dichloromethane to dichloromethane/ethyl acetate) afforded the products.

Ethyl (2-hydroxyimino)-3-(2-pyrrolyl)propanoate 9. From oxime **1a** and pyrrole; light brown solid (0.18 g; 45%); m.p.: 119.3-121.8 °C (from ethanol-hexanes; lit.⁸ m.p. 118-120 °C); ν_{\max} : 3390, 2988, 1720, 1189, 1026, 724; ^1H δ (300 MHz) 10.42 (1H, bs), 8.66 (1H, bs), 6.68-6.71 (1H, m), 6.04-6.07 (1H, m), 5.98-6.01 (1H, m), 4.30 (2H, q, J 6.9), 3.93 (2H, s), 1.34 (3H, t, J 6.9).

Ethyl 4a,6-dimethyl-4,4a,7,7a-tetrahydro-pyrrolo[2,3-*e*]-1,2-oxazine-3-carboxylate 10. From oxime **1a** and 2,5-dimethylpyrrole; oil (0.153 g, 34%); ν_{\max} : 2980, 1721, 1378, 1280, 1175, 1018; ^1H δ (300 MHz) 4.32 (2 H, q, J 7.1), 4.13 (1 H, dd, J 6.2, 1.4), 3.08 – 2.91 (1 H, m), 2.90 – 2.69 (2 H, m), 2.65 (1 H, d, J 6.5), 2.01 (3 H, s), 1.34 (3 H, t, J 7.1), 1.24 (3 H, s).

4a,7a-Dihydro-3-phenyl-4*H*-furo[2,3-*e*]-1,2-oxazine 13. From oxime **12** and furan; yellow solid (0.193 g; 48%); m.p.: 72.8-74.2 °C (from hexanes; lit.¹¹ m.p. 71-72 °C) ν_{\max} : 3059, 2982, 1612, 1446, 1244, 1059, 694; ^1H δ (300 MHz) 7.87 – 7.67 (2 H, m), 7.54 – 7.40 (3 H, m), 6.34 (1 H, d, J 10.9), 5.18 – 4.98 (2 H, m), 4.87 – 4.61 (1 H, m), 3.19 (1 H, dd, J 15.4, 3.2), 3.06 (1 H, dd, J 15.2, 2.9).

4-Chloro-6-ethoxy-5,6-dihydro-3-phenyl-4*H*-1,2-oxazine 15. From oxime **14** and ethyl vinyl ether; oil (0.196 g; 48%); ν_{\max} : 2964, 1751, 1673, 1223, 1041; ^1H δ (300 MHz) 7.63 (2 H, dd, J 6.7, 3.0), 7.32 (3 H, dd, J 4.8, 1.7), 5.29 – 5.07 (1 H, m), 4.71 (1 H, dd, J 6.6, 2.1), 3.89 – 3.74 (1

H, m), 3.56 (1 H, dq, J 9.8, 7.0), 2.68 – 2.32 (2 H, m), 1.15 (3 H, t, J 7.1); ^{13}C δ (75 MHz) 154.5, 133.6, 130.1, 128.6, 126.5, 94.1, 64.4, 39.3, 33.1, 15.1.

Ethyl pyrrole-2-(2-*t*-butoxycarbonylhydrazono)propanoate 17. From hydrazone **1b** and pyrrole; light brown solid (0.121 g, 41%); m.p.: 142–143.8 °C (from dichloromethane-hexanes; lit.¹³ 141 °C); ν_{max} : 3446, 3415, 1708, 1612; ^1H δ (300 MHz) 8.48 (1 H, bs), 8.29 (1 H, s), 6.70 (1 H, dd, J 4.1, 2.7), 6.10 (1 H, dd, J 5.9, 2.9), 6.04 (1 H, bs), 4.32 (2 H, q, J 7.1), 3.81 (2 H, s), 1.48 (9 H, s), 1.35 (3 H, t, J 7.1); ^{13}C δ (75 MHz) 165.8, 154.5, 145.0, 122.9, 118.5, 108.5, 107.2, 82.7, 62.3, 28.0, 24.8, 14.1.

***t*-Butyl 6-ethoxy-3-phenyl-1,4,5,6-tetrahydropyridazine-1-carboxylate 21.** From hydrazone **20** and ethyl vinyl ether; oil (0.164 g; 54%); ν_{max} : 2967, 1699, 1398, 1336, 1155, 1065; ^1H δ (300 MHz) 7.83 (2 H, dd, J = 7.6, 1.8), 7.57 – 7.30 (3 H, m), 5.71 (1 H, bs), 3.64 (2 H, q, J = 7.0), 2.91 – 2.51 (2 H, m), 2.32 – 2.09 (1 H, m), 1.80 (1 H, tdd, J = 13.4, 6.4, 2.5), 1.60 (9 H, s), 1.17 (3 H t, J = 7.0); ^{13}C δ (101 MHz) 154.4; 137.9, 129.9, 129.2, 128.5, 126.1, 125.6, 123.3, 101.0, 82.6, 63.5, 28.50, 28.41, 23.7, 22.5, 18.5, 15.4; HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_3$ 305.1865; found 365.1871.

***t*-Butyl 4-chloro-6-ethoxy-3-methyl-1,4,5,6-tetrahydropyridazine-1-carboxylate 24.** From hydrazone **23** and ethyl vinyl ether; oil (0.116 g, 42%); ν_{max} : 2979, 1702, 1397, 1255, 1148, 1021; ^1H δ (300 MHz) 9.52 (1 H, s), 5.64 (1 H, bs), 4.17 (1 H, d, J 6.7), 3.54 (2 H, q, J 7.0), 2.63 (1 H, ddd, J 15.6, 2.6, 0.8), 2.30 – 2.20 (1 H, m), 2.17 (3 H, s), 1.54 (9 H, s), 1.18 (3 H, t, J 7.0); ^{13}C δ (75 MHz) 154.7, 146.5, 94.0, 82.9, 64.3, 62.1, 39.5, 33.2, 18.2, 15.1. HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{22}\text{ClN}_2\text{O}_3$ 277.1319; found 277.1312.

Ethyl 3a,6a-dihydrofuro[2,3-*d*]isoxazole-3-carboxylate 25. From ethyl chlorooximidoacetate **4** and furan; oil (0.114 g, 31%); ν_{max} : 1747, 1625, 1475, 1244, 1056; ^1H δ (300 MHz) 6.62 – 6.52 (1 H, m), 6.04 – 5.95 (2 H, m), 5.34 – 5.29 (1 H, m), 4.33 (2 H, q, J 7.1), 1.32 (3 H, t, J 7.1); ^{13}C δ (75 MHz) 160.0, 150.4, 149.6, 100.7, 91.7, 87.1, 62.5, 14.3.

Ethyl 3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazole-3-carboxylate 26. From ethyl chlorooximidoacetate **4** and dihydrofuran; oil (0.237 g, 64%); ν_{max} : 2986, 1722, 1264, 1136, 1089, 1037. ^1H δ (300 MHz) 6.28 (1 H, d, J 6.3), 4.41 – 4.23 (2 H, m), 4.14 – 3.89 (1 H, m), 3.89 – 3.74 (1 H, m), 3.53 (1 H, ddd, J 12.0, 9.0, 5.3), 2.32 – 2.14 (1 H, m), 1.34 (3 H, t, J 7.1); ^{13}C δ (75 MHz) 160.0, 152.2, 110.7, 66.6, 50.4, 29.9, 13.9.

Diethyl 4,5-dihydroisoxazole-3,4-dicarboxylate 27. From ethyl chlorooximidoacetate **4** and ethyl acrylate; oil (0.211 g, 49%); ν_{max} : 2988, 1737, 1439, 1258, 1067; ^1H δ (400 MHz) 5.20 (1 H, dd, J 11.0, 8.3), 4.35 (2 H, dt, J 14.3, 5.0), 4.11 (2 H, q, J 7.1), 3.50 (2 H, dd, J 9.7, 2.8), 1.36 (3 H, td, J 7.1, 4.5), 1.25 (3 H, t, J 7.1).

Ethyl 2-(hydroxyimino)-2-(1*H*-pyrrol-2-yl)acetate 28. From ethyl chlorooximidoacetate **4** and pyrrole; yellowish solid (0.167 g; 48%); m.p.: 147.3–149.4 °C (from dichloromethane-hexanes; lit.⁹ 148–150 °C); ν_{max} : 3432, 3194, 1713, 1126, 1034; ^1H δ 11.32 (1 H, bs), 11.06 (1 H, bs), 7.11 – 7.06 (1 H, m), 6.90 (1 H, dd, J 7.5, 1.4), 6.21–6.18 (1 H, m), 4.36 (2 H, q, J 5.9), 1.36 (3 H, t, J 5.9).

Acknowledgements

The authors thank Prof. Filipa Ribeiro and Dr. Auguste Fernandes for the nitrogen adsorption measurements. Financial support by FCT, for acquisition of XRD equipment, under project REEQ/700/CTM/2005, is also gratefully acknowledged.

References

1. Reviews: (a) Debecker, D. P.; Gaigneaux, E. M.; Busca, G. *Chem. Eur. J.* **2009**, *15*, 3920. (b) Centi, G.; Perathoner, S. *Micropor. Mesopor. Mat.* **2008**, *107*, 3. (c) Figueras, F.; Kantam, M. L.; Choudary, B. M. *Curr. Org. Chem.* **2006**, *10*, 1627. (d) Figueras, F. *Top. Catal.* **2004**, *29*, 189.
2. Climent, M. J.; Corma, A.; Iborra, S.; Epping, K.; Velty, A. *J. Catal.* **2004**, *225*, 316.
3. (a) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; John Wiley & Sons, Ltd: Chichester, 2002. (b) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH: Weinheim, 2001.
4. Reviews: (a) Lemos, A. *Molecules* **2009**, *14*, 4098. (b) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149. (c) Lyapkalo, I. M.; Ioffe, S. *Russ. Chem. Rev.* **1998**, *67*, 467. (d) Gilchrist, T. L.; Wood, J. E. In *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J. Ed.; Pergamon Press: Oxford, 1996, Vol. 6, pp. 279-299. (e) Gilchrist, T. L. *Chem Soc. Rev.* **1983**, *12*, 53.
5. Reviews: (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusano, S. *Eur. J. Org. Chem.* **2009**, 3109. (b) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusano, S. *Arkivoc* **2002**, (xi), 274. (c) Attanasi, O. A.; Filippone, P. *Synlett* **1997**, 1128.
6. (a) Rai, K. M. L. *Top. Heterocycl. Chem.* **2008**, *13*, 1. (b) Jäger, V.; Colinas, P. A. in *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H. Eds.; John Wiley & Sons, Inc.: New York, 2002, Vol. 59, pp. 363-472. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (d) Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. In *Cycloaddition Reactions of Nitrile Oxides with Alkenes*; Katritzky, A. R., Ed.; *Adv. Heterocycl. Chem.* **1994**, *60*, 261. (e) Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, pp. 291-392.
7. Lemos, A.; Lourenço, J. P. *Tetrahedron Lett.* **2009**, *50*, 1311.
8. Gilchrist, T. L.; Lemos, A. *Tetrahedron* **1992**, *48*, 7655.
9. Gilchrist, T. L.; Lemos, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1391.
10. (a) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1283. (b) Gilchrist, T. L.; Lingham, D.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, 1089.
11. Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 249.

12. Zimmer, R.; Angermann, J.; Hain, U.; Hiller, F.; Reissig, H.-U. *Synthesis* **1997**, 1467.
13. Clarke, S. J.; Gilchrist, T. L.; Lemos, A.; Roberts, T. G. *Tetrahedron* **1991**, 47, 5615.
14. Conti, D.; Rodriguez, M.; Sega, A.; Taddei, M. *Tetrahedron Lett.* **2003**, 44, 5327.
15. Yang, S.; Hayden, W.; Griengl, H. *Monatsh. Chem.* **1994**, 125, 469.
16. Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, 48, 366.
17. Reddy, V. V. R. *Synlett* **2005**, 363.
18. Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, 47, 2147.
19. Masaki, M.; Fukui, K.; Ohta, M. *J. Org. Chem.* **1967**, 32, 3564.
20. Yoon, S. C.; Cho, J.; Kim, K. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 109.