Tetrahedron Letters 50 (2009) 1311–1313

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Hydrotalcite catalysed [4+2] cycloaddition reactions of nitroso- and azo-alkenes

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ARTICLE INFO

Article history:
Received 28 November 2008
Revised 18 December 2008
Accepted 9 January 2009
Available online 15 January 2009

Keywords:
Hydrotalcite
Catalysis
Nitrosoalkene
Azoalkene
Cycloaddition
1,2-Oxazine
Pyridazine

ABSTRACT

The generation of nitroso- and azo-alkenes and their [4+2] cycloaddition reactions with furan and ethyl vinyl ether, producing dihydro-1,2-oxazines and tetrahydropyridazines, by the use of catalytic Mg:Al 3:1 hydrotalcite, is described. The absence of an organic solvent, the catalytic quantities of Ht required together with its regeneration and reuse, may be regarded as environmentally friendly, greener and economically advantageous over the usual methods.

Hydrotalcite-like (Hts) anionic clays belong to the class of double hydroxide minerals (LDHs) with the general formula $M_x^{2+}M_y^{3+}(OH)_{2(x+y)}A_{y/n}^{n-} \cdot mH_2O$, where M^{2+} and M^{3+} are divalent and trivalent metals, respectively, and A^{n-} is an intercalated anion. In the case of magnesium and aluminium as the metals these materials are structurally described as brucite-like ($Mg(OH)_2$) sheets where various Mg^{2+} are isomorphously substituted by trivalent Al^{3+}. The positive charge generated by the presence of the trivalent cation in the layer is compensated by the intercalated anion.[1] These compounds are usually prepared by coprecipitation followed by an ageing time and/or a hydrothermal treatment to improve the crystallinity.[2] Thermal treatments convert LDHs into mixed oxides with high surface area and strong basic properties.

The basic properties of mixed oxides obtained by calcination of hydrotalcites are mainly associated with the Lewis basicity of the pairs O^{2-} Mg^{2+} (in the case of Mg–Al mixed hydroxides). A controlled rehydration promotes a structural rearrangement, resulting in a Meixnerit-like compound by a reconstruction process using a memory effect and giving rise to a change in the nature of the basic sites.[3] In this case, the basic properties are influenced by the presence of intercalated hydroxide anions.

Due to the ability of changing the nature of the basic sites by controlled hydration procedures, these solids show a great potential to be used as catalysts for reactions that need Lewis basic sites, Brønsted basic sites or even pairs of acid-base sites.

Likewise, in recent years, Hts have found applications in aldol and Knoevenagel condensations, in Michael, Wadsworth–Emmons, nitroaldol, N-oxidation and trans-esterification reactions,[4] and in [3+2] cycloaddition reactions that are used for the synthesis of isoxazoles[5] and tetrazoles.[6]

Over the last decades, the use of electron deficient nitroso–[7,8] and azo-alkenes or 1,2-diaza-1,3-butadienes,[9,10] in inverse electron demand Diels–Alder cycloaddition reactions, has successfully provided routes to a large number of new 1,2-oxazine and pyridazine derivatives. Amongst the class of heterocyclic compounds containing nitrogen, these heterocycles have proved to be useful targets, not only due to their biological and pharmacological properties but especially because of their wide and versatile use as synthetic intermediates.[11,12]

Base induced dehydrohalogenation of α-halo-oximes and -hydrazones **I** constitutes the general method for the generation of nitroso- and azo-alkenes **II**. Their interception 'in situ' by a wide range of nucleophilic olefins or heterocycles produces the cycloadducts **III** in highly regioselective fashion (Scheme 1). In order for the reaction be efficient a low concentration of the transient nitroso- or azo-alkene and concomitantly a great excess of the dienophile (usually a 10-fold mol equiv) are required. These conditions are commonly attained using a substantial volume of organic solvent and an inorganic base, the low solubility of which ensures a slow rate of dehydrohalogenation.

During our studies on the catalytic application of Hts, we became interested in the possibility of their use as a dehydrohalogenating agent for α-bromo oximes or hydrazones **1**. We were pleased to find that mixing the oxime or hydrazone with a 10 mass % of

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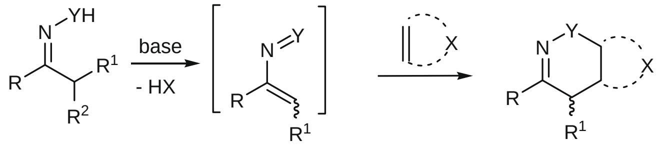
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.045

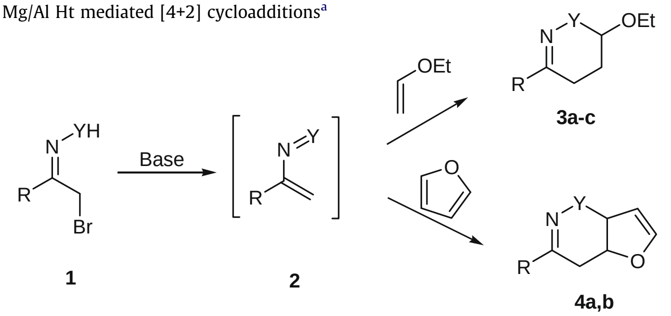


I **II** **III**

R = CF_3; CHO; COR^3; CO_2R^4; C_6H_5; 4-$NO_2C_6H_4$; $P(O)(OR^5)_3$; Me
R^1 = H; Cl; $P(O)(OR^6)_3$; $P(O)Ph_3$
R^2 = Br; Cl
Y = O; N-CO_2R^5; N-$C_6H_4(NO_2)_2$-2,4; N-$SO_2C_6H_4$Me-4
X = NR^7; O; CH_2

Scheme 1. Synthesis of 1,2-oxazines and pyridazines by cycloaddition reactions of nitroso- and azo-alkenes.

Table 1
Mg/Al Ht mediated [4+2] cycloadditions[a]



Entry	R	Y	Base	Product	Yield (%)	(%)^{lit}
1	CO_2Et	O	Ht	**3a**	54	**(99)**[8h]
2	CO_2Et	O	Ht	**4a**	21	**(46)**[13]
3	Ph	O	Ht	**3b**	48	**(87)**[14]
4	CO_2Et	NCO_2CMe_3	Ht	**3c**	80	**(98)**[15]
5	CO_2Et	NCO_2CMe_3	Ht	**4b**	58	**(100)**[15]
6	CO_2Et	NCO_2CMe_3	—	—	—	
7	CO_2Et	NCO_2CMe_3	Na_2CO_3	—	—	
8	CO_2Et	O	Ht[b]	**3a**	51	
9	CO_2Et	NCO_2CMe_3	Ht[b]	**3c**	82	

[a] Reaction conditions: oxime or hydrazone (1 mmol), Mg/Al hydrotalcite (10% mass equiv), dienophile (10 mmol), water (2 drops), rt, 16 h.
[b] Regenerated and reused Mg/Al hydrotalcite.

calcinated hydrotalcite,[16] in the presence of 10 mol equiv of dienophile and two drops of water, afforded the expected cycloadducts in reasonable to good yields (Table 1).[17] The addition of water was necessary, presumably to rehydrate the Ht, since in reactions conducted in its absence no product could be detected or isolated. Also, in control reactions performed in the absence of Ht, no reaction products were detected (entry 6).

On replacing calcinated Mg:Al 3:1 Ht by sodium carbonate under the same reaction conditions, that is, no solvent, 10 mass % with or without two drops of water, no reaction products were isolated (entry 7).

The Mg:Al 3:1 Ht filtered from the reaction media, washed with water and acetone, dried and calcinated (500 °C under a flux of dry air), could be used again without loss of activity (entries 8 and 9).

In summary, we have outlined a simple and effective method for the generation of nitroso- and azo-alkenes by the catalytic use of calcined Mg/Al 3:1 hydrotalcite and its cycloaddition reactions with furan and ethyl vinyl ether, producing 5,6-dihydro-4*H*-1,2-oxazines and 1,4,5,6-tetrhydropyridazines. The yields obtained by this methodology, although somewhat lower than those obtained by the commonly used strategy, are reasonable to good. The advantages of the present methodology are the elimination of both organic solvent and large excess of an inorganic base. Moreover, the ease of recovery and reuse of the hydrotalcite may be regarded as a valuable contribution to environmental friendly and greener process.

Further studies on the optimisation of the reaction conditions as well the broadening the scope and application to other 4π hetero Diels–Alder partners are underway.

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16. Procedure for Mg/Al hydrotalcite: 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 $Mg(NO_3)_2$ and 0.037 mol of $Al(NO_3)_3$ under stirring at room temperature. The gel was left for 18 h at 80 °C. The hydrotalcite was recovered by centrifugation, washed until pH 7 and dried at 80 °C overnight. Before the catalytic tests, the hydrotalcite was activated at 450 °C under a flux of dry nitrogen for 6 h.
17. Representative procedure for compound **3c**: To the mixture of hydrazone 0.31 g (1 mmol) and ethyl vinyl ether (10 mmol), were added 0.03 g Ht (10 wt %) and two drops of water. After stirring for 16 h, the Ht was filtered off. Dry-flash chromatography of the filtrate (increasing polarity dichloromethane to dichloromethane/ethyl acetate : 3/1) afforded the pyridazine **3c** as a white solid (0.24 g; 80%). mp: 65.8–67.4 (from hexanes; lit.[13] mp 66–68 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (s, 1H), 4.36–4.12 (m, 2H), 3.55 (q, J = 6.9, 2H), 2.60 (dd, J = 5.8, 18.7, 1H), 2.50–2.33 (m, 1H), 2.05 (dd, J = 13.0, 19.3, 1H), 1.59 (d, J = 62.8, 10H), 1.39–1.22 (m, 3H), 1.09 (t, J = 7.0, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.28, 152.33, 142.45, 82.93, 76.91, 63.73, 61.71, 28.19, 22.71, 17.47, 15.23, 14.21; IR (KBr cm^{-1}): 2998, 1711, 1607, 1335, 1270, 1159, 1080.