ONE-STEP FORMATION OF N-ALKENYL-MALONAMIDES AND N-ALKENYL-THIOMALONAMIDES FROM CARBAMOYL MELDRUM'S ACIDS.

Paweł Punda and Sławomir Makowiec*

Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology,

Narutowicza 11/12; Gdańsk 80-952, Poland;

E-mail: mak@pg.gda.pl, Tel/Fax: +48 58 3472694

Received

ABSTRACT: A one-pot synthesis for the preparation of N-alkenyl-malonamides and N-alkenyl-thiomalonamides was developed. 5-[Hydroxy/mercapto(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione act as a source of ketenes that react with the tautomeric form of alkyl-(2-phenyl-propylidene)-amines. A possible [2+2] or [4+2] cycloaddition product of ketene to imines was not observed.

KEYWORDS: amides, acylations, tautomerism, ketenes, Meldrum's acid

INTRODUCTION

Meldrum acid derivatives are widely used in organic synthesis[1], the mainstream of applications is due to the fact that the 3-substituted-1,3-dioxadiones are a potential source of ketene in the course of thermolysis[2]. Among them acyl Meldrum acids play the most significant role as a starting material for structurally diverse compounds as: 3-substituted-β-lactams[3], isooxazolols[4], pilicides[5], 1,3-oxazinones[6], pyrones[7] and derivatives of tetramic acid[8].

Recently we have focused our efforts on the application of particular derivatives of Meldrum acids means 5-[hydroxy(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-

diones **1a** in organic synthesis. During thermal decomposition **1a** is a source of carbamoylketenes, which, as demostrated by Pak[9] and our own research, may acylate amines, alcohols and thiols[10]. Moreover, carbamoylketenes generated from **1a** as with other ketenes could undergo [2+2] cycloaddition with aldimines leading to the formation of 1,4-disubstituted-2-oxoazetidine-3-carboxylic acid amides[11].

Our previous research on the reactivity of **1a** was limited to non-enolizable aldimines. However, experiments performed by Almqvist[5] with ketenes genereated from acyl Meldrum acids and thiazolines with acidic protons in α-position showed the formation of unexpected 2-pyridinones as a product, whereas the same acyl ketenes generated in the same way by Yamamoto react with non-enolizable aldimines giving [2+2] or [4+2] cycloaddition product[12].

In addition, Trogolo and co-workers have explored the reaction of ketenes generated from 2,2,6-trimethyl-4H-1,3-dioxin-4-one with enolizable aldimines and observed exclusively the formation of N-alkenyl-3-ketoamides but no products of [4+2] or [2+2] cycloadition[13]. The results obtained by Trogolo and Almquist inspired us to check which product will be formed in the reaction of carbamoylketenes or thicarbamoylketenes obtained from 5-[hydroxy/mercapto(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **1a-d** during thermal decomposition in the presence of enolizable aldimines. Because the analysis of literature data as well as our own experience with carbamoylketenes suggest the possibility of creating four different products among which the formation of N-alkenyl-(thio)malonamides or 4-amino-2-pyridinones seems the most likely (Scheme 1).

RESULTS NAD DISCUSION

For a model of enolizable aldimines with well known equilibrum between imine and enamine we chose alkyl-(2-phenyl-propylidene)-amines **2** described by Krohnke[14] which was also used in experiments performed by Trogolo.

In the first experiment we heat in boiling toluene 1 eq of **1a** with 1 eq iso-propyl-(2-phenyl-propylidene)-amine **2a** until disappearance of **1a** what take approximately 3 h. We choose toluene as a solvent because of the optimal rate of decomposition of **1a**, when using lower boiling solvents, decomposition of **1a** takes up to 28 h, while the higher boiling solvents may result in the formation of by-products[11]. From the reaction mixture after chromatographic purification we isolated N-isopropyl-N'-phenyl-N-[(1E)-2-phenyl-prop-1-enyl]-malonamide **3aa** as the only product in 37% yield (Scheme 2, Table 1, entry 1). Our previous experience with trapping carbamoylketenes[10], [11], suggested to us that using an excess of nucleophile may help increase the yield of reaction. For this purpose we next made two experiments with the same combination of reagent and in the same conditions but using a higher ratio of enolizable aldimine, 2 and 4 eq respectively. In both cases after purification we obtain the same 60% yield of **3aa** which indicates achieving the maximum due to this parameter at 2 eq of aldimine. It should be noted that in all these experiments we observed the formation in significant amounts of yielow-brown tar which remained on the silica gel during flash chromatography. To check the scope and limitation of the reaction under investigation we decided to perform a series of experiments with other derivative of alkyl-(2-phenyl-propylidene)-amines as well as with Meldrum acid derivatives containing on nitrogen 3-chlorophenyl or ethyl group, using 2 eq of aldimine per 1eq of **1**. In all these experiments we obtained N-alkenyl-malonamides with good to moderate yields (entries 5, 7-14) with the exception of the reaction of **1b** with **2c** where the product required chromatographic purification three times what caused low yield (entry 11).

On the other hand, our experience with the reaction of secondary amine with carbamoylketenes showed that the use of TMS-Cl as an additive to the reaction mixture colud strongly increase yield of amide [10]. We refluxed in boiling toluene 1eq of **1a** with 2 eq of **2b** in the presence of 1.5eq of TMS-Cl obtaining malonylamide **3ab** with a worse yield than in the experiment without TMS-Cl (entry 6).

In the further course of research we checked whether the thicarbamoyloketenes generated from 5-[mercapto(methylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1d** can also acylate aldimines in the same manner. Also in this case, we noticed that appropriate N-alkyl-N-[(1E)-2-phenyl-prop-1-enyl]-2-methylthiocarbamoyl-acetamide **3da-dd** are formed with good yield when 1eq of **1d** is heated to reflux in toluene in the presence of 2 eq of **2** (entries 15 - 18).

As we pointed out at the beginning, one possible route of the reaction of aldimines with carbamoylketenes colud be [2+2] cycloaddition leading to the formation of β-lactams. Therefore, we carried out an experiment in conditions most conducive to the formation of β-lactams, meaning a reaction in boiling toluene saturated with HCl. However, we again obtain only N-alkenyl-malonamide **3aa** acompaing with lot of tar (entry 4).

The developed one-pot method of synthesis of N-alkenyl-malonamides and N-alkenyl-thiomalonamides eliminates the need for tedious preparation of 3-arylo/alkiloamino-3-oxopropanoic acids or 3-arylo/alkiloamino-3-thioxopropanoic acids or their chlorides in order to obtain suitable N-alkenyl-malonamides and N-alkenyl-thiomalonamides. The obtained N-alkenyl-malonamides, as with other known N-alkenyl-amides, should be a valuable substrat for various chemical transformation[15], their application in synthesis is under investigation in our laboratory.

ACKNOWLEDGMENT

Scientific work financed from funds for science in 2010-2011 as a research project NN204 088338

EXPERIMENTAL

N-Isopropyl-N'-phenyl-N-[(1E)-2-phenylprop-1-enyl]-malonamide (3aa). Sample experiment.

To a solution of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl -1,3-dioxane-4,6-dione (**1a**) (1) (526 mg, 2 mmol) in anhydrous toluene (10 ml) was added isopropyl-(2-phenyl-propylidene)-amine (**2a**) (701 mg, 4 mmol) was stirred under reflux by 3 h. After completion of the reaction the solvent was removed under vacuum, and the residue was purified by flash column chromatography (EtOAc-hexanes, 1:2) to give **3aa** (400 mg, 60%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.7 Hz, 6 H,), 2.00 (d, *J* = 1.25 Hz, 3 H), 3.45 (s, 2 H), 4.96 (hept, *J* = 6,7 Hz, 1 H), 6.28 (d, *J* = 1.25 Hz, 1 H), 7.1 (t, *J* = 7.3 Hz, 1 H), 7.26-7.49 (m, 7 H), 7.6 (d, *J* = 1.25 Hz, 2 H), 10.23 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.6, 20.3, 41.7, 47.6, 120.5, 121.3, 124.6, 126.7, 129.1, 129.2, 129.4, 138.4, 139.7, 142.8, 164.9, 168.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{24}N_2NaO_2$: 359.1735; found: 359.1745.

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