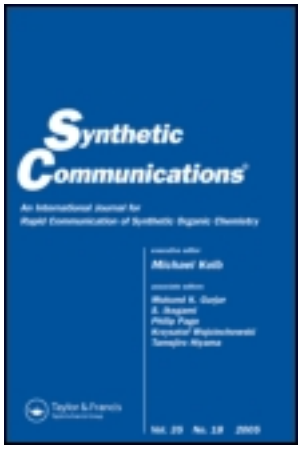


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 08 May 2012.Version of record first published: 05 Mar 2013.

To cite this article: Paweł Punda & Sławomir Makowiec (2013): One-Step Formation of N-Alkenyl-malonamides and N-Alkenyl-thiomalonamides from Carbamoyl Meldrum's Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:10, 1362-1367

To link to this article: http://dx.doi.org/10.1080/00397911.2011.634082

*Synthetic Communications*®, 43: 1362–1367, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.634082

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

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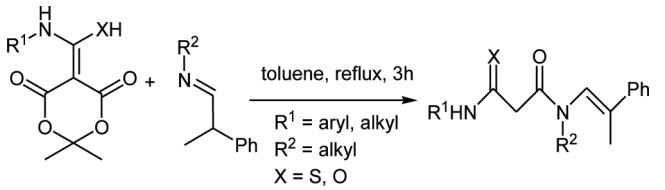
## GRAPHICAL ABSTRACT




**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** Acylations; amides; ketenes; Meldrum's acid; tautomerism



## INTRODUCTION

Meldrum acid derivatives are widely used in organic synthesis,[1] usually because 3-substituted-1,3-dioxadiones are a potential source of ketenes in the course of thermolysis.[2] Among them, acyl Meldrum acids play the most significant role as a starting material for structurally diverse compounds such 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, 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 Lee et al.[9] and our own research, may

Received September 12, 2011.
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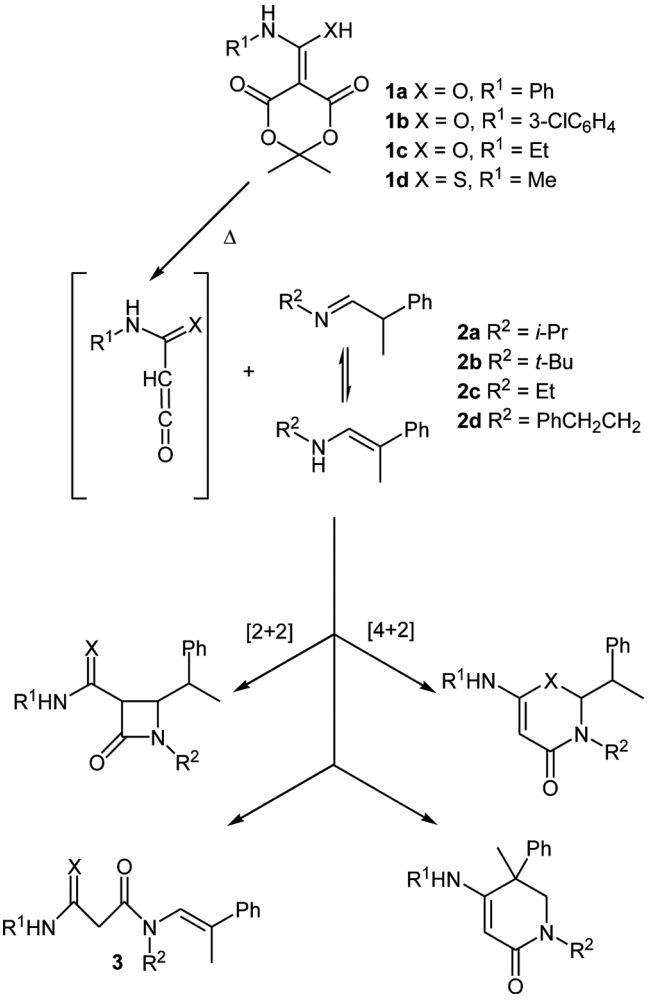
acylate amines, alcohols, and thiols.[10] Moreover, carbamoylketenes generated from **1a** as with other ketenes could undergo [2 + 2] cycloaddition with aldimines, leading to the formation of 1,4-disubstituted-2-oxoazetidine-3-carboxylic acid amides.[11]

Our previous research on the reactivity of **1a** was limited to nonenolizable aldimines. However, experiments performed by Emtenas et al.[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 nonenolizable aldimines giving [2 + 2] or [4 + 2] cycloaddition product.[12]

In addition, Trogolo and coworkers 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






**Scheme 1.** Possible routes of reaction of carbamoyl ketenes or thiocarbamoylketenes with alkyl-(2-phenyl-propylidene)-amines.

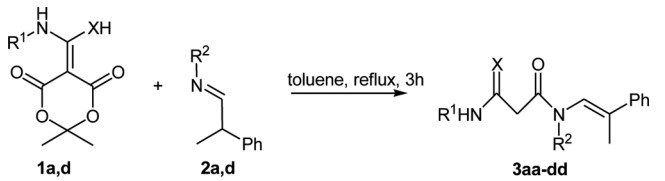
[4 + 2] or [2 + 2] cycloadition.[13] The results obtained by Trogolo and Almquist inspired us to check which product will be formed in the reaction of carbamoylketenes or thicarbamoylketenes obtained from 5-[hydroxy/mercapto(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **1a–d** during thermal decomposition in the presence of enolizable aldimines. The analysis of literature data as well as our own experience with carbamoylketenes suggests 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 AND DISCUSSION

For a model of enolizable aldimines with well-known equilibrum between imine and enamine we chose alkyl-(2-phenyl-propylidene)-amines **2**, described by Ahlbrecht et al.,[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**, which takes 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 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 greater ratio of enolizable aldimine, 2 and 4 eq., respectively. In both cases, after purification we obtained the same 60% yield of **3aa**, which indicates that the maximum is achieved at 2 eq. of aldimine. It should be noted that in all these experiments we observed the formation in significant amounts of yellow-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 derivatives of alkyl-(2-phenyl-propylidene)-amines as well as with Meldrum acid derivatives containing nitrogen 3-chlorophenyl or ethyl group, using 2 eq. of aldimine per 1 eq. of **1**. In all these experiments we obtained N-alkenyl-malonamides with good to moderate yields (entries 5 and 7–14) with the exception of the reaction of **1b** with **2c**, where the product required chromatographic purification three times, which caused a poor 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




**1a,d** **2a,d** **3aa-dd**

**Scheme 2.** Synthesis of N-alkenyl-malonamides and N-alkenyl-thiomalonamides.

**Table 1.** Synthesis of N-alkenyl-malonamides and N-alkenyl-thiomalonamides

| Entry | 1 | $R^1$ | X | 2 | $R^2$ | Product 3 | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1[a] | **a** | Ph | O | **a** | *i*-Pr | **3aa** | 37 |
| 2 | **a** | Ph | O | **a** | *i*-Pr | **3aa** | 60 |
| 3[b] | **a** | Ph | O | **a** | *i*-Pr | **3aa** | 60 |
| 4[c] | **a** | Ph | O | **a** | *i*-Pr | **3aa** | 21 |
| 5 | **a** | Ph | O | **b** | *t*-Bu | **3ab** | 47 |
| 6[d] | **a** | Ph | O | **b** | *t*-Bu | **3ab** | 40 |
| 7 | **a** | Ph | O | **c** | Et | **3ac** | 41 |
| 8 | **a** | Ph | O | **d** | $PhCH_2CH_2$ | **3ad** | 48 |
| 9 | **b** | 3-$ClC_6H_4$ | O | **a** | *i*-Pr | **3ba** | 56 |
| 10 | **b** | 3-$ClC_6H_4$ | O | **b** | *t*-Bu | **3bb** | 60 |
| 11 | **b** | 3-$ClC_6H_4$ | O | **c** | Et | **3bc** | 22 |
| 12 | **b** | 3-$ClC_6H_4$ | O | **d** | $PhCH_2CH_2$ | **3bd** | 40 |
| 13 | **c** | Et | O | **a** | *i*-Pr | **3ca** | 63 |
| 14 | **c** | Et | O | **b** | *t*-Bu | **3cb** | 57 |
| 15 | **d** | $CH_3$ | S | **a** | *i*-Pr | **3da** | 49 |
| 16 | **d** | $CH_3$ | S | **b** | *t*-Bu | **3db** | 47 |
| 17 | **d** | $CH_3$ | S | **c** | Et | **3dc** | 55 |
| 18 | **d** | $CH_3$ | S | **d** | $PhCH_2CH_2$ | **3dd** | 32 |

[a]1 eq of **2a** was used.
[b]4 eq of **2a** was used.
[c]1 eq of **2a** was used and the reaction mixture was saturated with HCl.
[d]1.5 eq of TMS-Cl was added.



mixture could strongly increase yield of amide.[10] We refluxed in boiling toluene 1 eq. of **1a** with 2 eq. of **2b** in the presence of 1.5 eq. 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 1 eq. 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** acompanied by lots 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, 3-arylo/alkiloamino-3-thioxopropanoic acids, or their chlorides 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 substrate for various chemical transformation.[15] Their application in synthesis is under investigation in our laboratory.

## EXPERIMENTAL

Isopropyl-(2-phenyl-propylidene)-amine (**2a**) (701 mg, 4 mmol) was added to a solution of 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1a**) (526 mg, 2 mmol) in anhydrous toluene (10 ml), which was stirred under reflux for 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, $CDCl_3$): $\delta = 1.20$ (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, $CDCl_3$): $\delta = 16.6$, 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.



## ACKNOWLEDGMENT

Scientific work was financed from Funds for Science in 2010–2011 as research project NN204 088338.

## REFERENCES

1. Ivanov, A. S. Meldrum's acid and related compounds in the synthesis of natural products and analogs. *Chem. Soc. Rev.* **2008**, *37*, 789–811.
2. (a) Adediran, S. A.; Cabaret, D.; Lohier, J. F.; Wakselman, M.; Pratt, R. F. Substituted aryl malonamates as new serine $\beta$-lactamase substrates: Structure-activity studies. *Bioorgan. Med. Chem.* **2010**, *18*, 282–291; (b) Fillion, E.; Fishlock, D. Scandium triflate–catalyzed intramolecular Friedel–Crafts acylation with Meldrum's acids: Insight into the mechanism. *Tetrahedron.* **2009**, *65*, 6682; (c) Fillion, E.; Dumas, A. M. Synthesis of fused 4,5-disubstituted indole ring systems by intramolecular Friedel–Crafts acylation of 4-substituted indoles. *J. Org. Chem.* **2008**, *73*, 2920; (d) Shtaiwi, M.; Wentrup, C. Iminopropadienones from dioxanediones, isoxazolopyrimidinones, pyridopyrimidinones, and pyridopyrimidinium olates. *J. Org. Chem.* **2002**, *67*, 8558; (e) Wentrup, C.; Rao, R.; Frank, W.; Fulloon, B. E.; Moloney, D. W.J.; Mosandl, T. Aryliminopropadienone–C-amidoketenimine–amidinoketene-2-aminoquinolone cascades and the ynamine–isocyanate reaction. *J. Org. Chem.* **1999**, *64*, 3608.
3. Yamamoto, Y.; Watanabe, Y. 1,3-Oxazines and related compounds, XIV: Facile synthesis of 2,3,6-trisubstituted 2,3-dihydro-1,3-oxazine-5-carboxylic acids and 1,4-disubstituted 3-acyl-β-lactams from acyl Meldrum's acids and Schiff bases. *Chem. Pharm. Bull.* **1987**, *35*, 1871.
4. Sorensen, U. S.; Falch, E.; Krogsgaard-Larsen, P. A novel route to 5-substituted 3-isoxazolols: Cyclization of N,O-diBoc β-keto hydroxamic acids synthesized via acyl Meldrum's acids. *J. Org. Chem.* **2000**, *65*, 1003.
5. (a) Emtenas, H.; Alderin, L.; Almqvist, F. An enantioselective ketene–imine cycloaddition method for synthesis of substituted ring-fused 2-pyridinones. *J. Org. Chem.* **2001**, *66*, 6756; (b) Sellstedt, M.; Almqvist, F. Synthesis of a novel tricyclic peptidomimetic scaffold. *Org. Lett.* **2008**, *10*, 4005.
6. Pemberton, N.; Emtenäs, H.; Boström, D.; Domaille, P. J.; Greenberg, W. A.; Levin, M. D.; Zhu, Z.; Almqvist, F. Cycloaddition of Δ2-thiazolines and acyl ketenes under

acidic conditions results in bicyclic 1,3-oxazinones and not 6-acylpenams as earlier reported. *Org. Lett.* **2005**, *7*, 1019.
7. Lokot, I. P.; Pashkovsky, F. S. Lakhvich, F. A. A new approach to the synthesis of 3,6- and 5,6-dialkyl derivatives of 4-hydroxy-2-pyrone: Synthesis of rac-germicidin. *Tetrahedron* **1999**, *55*, 4783.
8. Pirc, S.; Bevk, D.; Jakše, R.; Rečnik, S.; Golič, L.; Golobič, A.; Meden, A.; Stanovnik, B.; Svete, J. Synthesis of N-substituted 3-aminomethylidenetetramic acids. *Synthesis* **2005**, *17*, 2969.
9. Lee, H. L.; Lee, J. P.; Lee, G. H.; Pak, Ch. S. Convenient synthesis of unsymmetric N,N'-disubstituted malondiamides mediated by Meldrum's acid. *Synlett.* **1996**, *12*, 1209.
10. Janikowska, K.; Makowiec, S. TMSCl as a rate-accelerating additive in acylations of amines with 5-(α-amino-α′-hydroxy)methylene Meldrum's acid. *Synth. Commun*, **2012**, *42*(7), 975.
11. Janikowska, K.; Pawelska, N. Makowiec, S. One-step synthesis of β-lactams with retro-amide side chain. *Synthesis* **2011**, *1*, 69.
12. Yamamoto, Y.; Watanabe, Y.; Ohnishi, S. 1,3-Oxazines and related compounds, XIII: Reaction of acyl Meldrum's acids with Schiff bases giving 2,3-disubstituted 5-acy1–3,4,5,6-tetrahydro-2H-1,3-oxazine-4,6-diones and 2,3,6-trisubstituted-2,3-dihydro-1,3-oxazin-4-ones. *Chem. Pharm. Bull.* **1987**, *35*, 1860.
13. Annibale, A. D.; Pesce, A.; Resta, S.; Trogolo, C. Reaction of 2,2,6-trimethyl-4H-1,3-dioxin-4-one with imines: An easy route to enamides. *Tetrahedron Lett.* **1996**, *37*, 7429.
14. Ahlbrecht, H.; Blecher, J.; Kronke, F. Vinylamine—VIII: Die kondensation von hydratropaaldehyd mit primären aminen. *Tetrahedron* **1971**, *27*, 2169.
15. Lenz, G. R. The photochemistry of enamides. *Synthesis* **1978**, *7*, 489.