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Reaction of 2,2,6-Trimethyl-4H-1,3-dioxin-4-one With Imines: an Easy Route to Enamides.

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Abstract: N-alkenyl acetoacetamides can be simply obtained in good yields by reaction of acetylketene, generated by thermolysis of 2,2,6-trimethyl-4H-1,3-dioxin-4-one in refluxing toluene, with imines possessing an α-hydrogen atom. Copyright © 1996 Elsevier Science Ltd

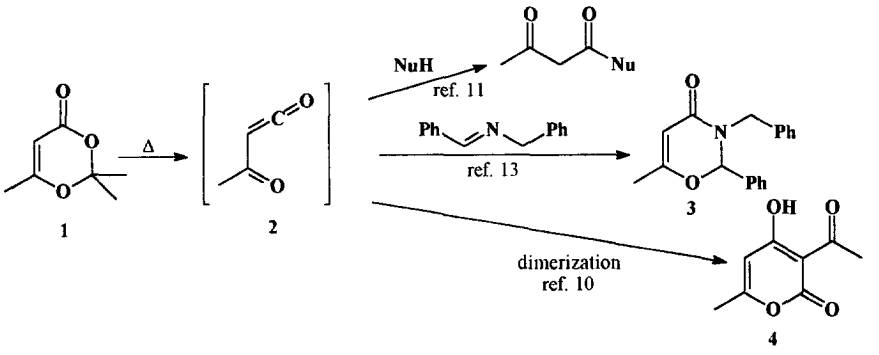
N-Alkenyl amides (enamides) are an interesting class of organic compounds that have found wide application in organic synthesis. Their importance as intermediates in a great number of synthetic trasformations, mostly photochemical, has been widely described.[1,2,3] In recent times great relevance was given also to the radical cyclization of enamides to azetidin-2-ones, reported by several groups.[4,5,6]

Usual experimental procedures for the synthesis of enamides involve, as the most general route, the acylation of an imine with an acid chloride (or anhidride) in presence of a base.[1] Nevertheless, the use of acetoacetyl chloride as the precursor of acetoacetyl enamides is not straightforward. In fact, its general preparation from diketene, a rather toxic reagent, is really difficult and so is its subsequent manipulation.[7]

In the light of our research on the reactivity of variously substituted enamides in free radical reactions,[8] we decided to develop a new synthetic route to acetoacetyl enamides, using synthetic analogues of diketene for the acylation of particularly substituted imines. Then we chose 2,2,6-trimethyl-4H-1,3-dioxin-4-one **1**, the "diketene-acetone adduct", a commercially available and inexpensive reagent.

As described in the literature, thermolysis of **1** above 100°C yields acetylketene[9,10,11] **2**, a powerful acetoacetylating agent that readily acylates OH, SH, and NH groups affording acetoacetic acid derivatives (Scheme 1). Species containing a C=N bond such as imines, carbodiimides or isocyanates have been reported to react with dioxinone **1** and related species.[12-16] Truly all previously reported examples of reactions between dioxinones and aldimines involve aromatic imines (usually derived from benzaldehyde) with no hydrogen adiacent to the C=N carbon. In these cases the involved products are generally oxazine derivatives.[12-13] These transformations are reported to proceed through a cycloaddition mechanism.[12a] For instance, reaction between **1** and the benzyl imine from benzaldehyde in a [4+2] mode provides oxazine **3** as reported in Scheme 1.

Scheme 1.



On the contrary when the reaction was carried out on imines from both aromatic and non aromatic ketones the formation of pyridones was observed.[13] Starting from the fact that no reports were found in literature about the reaction of **1** with imines from non aromatic aldehydes, we decided to investigate their reactivity towards **1** in the same experimental conditions described by other Authors. When we reacted the benzyl imine of hydratropaldehyde **5a** with **1** the only product isolated was enamide **6a** (Scheme 2).[17] In a similar way enamides **6b-j** were obtained from imines **5b-j** in modest to good yields, as summarized in Table 1.[18] Low yields in enamides **6f** and **6g** have probably to be ascribed to the instability of the starting imines. Variable amounts of aldehydes (derived from decomposition of unreacted imines during chromatographic purification of products) were usually isolated, together with minor amounts of dehydroacetic acid **4**, produced by dimerization of acetylketene (Scheme 1).[10] In no cases oxazines were isolated as final products.

Scheme 2.

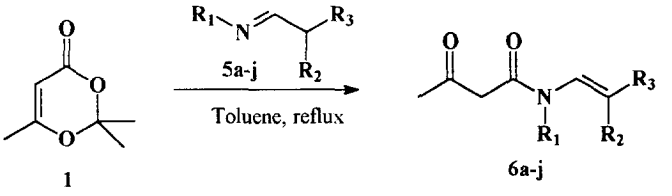


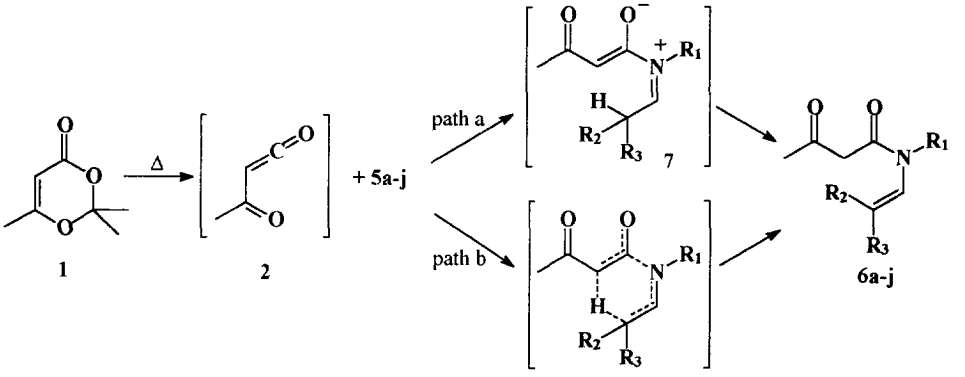
Table 1. Reactions of Imines with 2,2,6-Trimethyl-4H-1,3-dioxin-4-one.

Imine	R_1	R_2	R_3	Enamide	Yield %[a]
5a	CH_2Ph	Ph	Me	**6a**	65
5b	n-Propyl	Ph	Me	**6b**	54
5c	Isopropyl	Ph	Me	**6c**	57
5d	Cyclohexyl	Ph	Me	**6d**	52
5e	t-Butyl	Ph	Me	**6e**	45
5f	CH_2Ph	Ph	H	**6f**	10[b]
5g	CH_2Ph	CH_2SPh	Ph	**6g**	26
5h	CH_2Ph	CH_2SPh	Me	**6h**	70
5i	$CH(CH_3)Ph$	CH_2SPh	Me	**6i**	60
5j	$CH(CH_2Ph)CO_2Me$	CH_2SPh	Me	**6j**	65

a: yields refer to isolated, chromatographically pure compounds and are not optimized.
b: inseparable mixture of products, yield is estimated on the basis of the NMR spectrum of crude product.

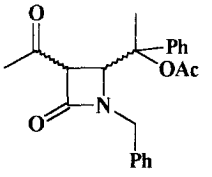
Our reactions showed to be less sensitive to the increasing steric hindrance of the alkyl group R_1 present in the aldimines than those leading to oxazines formation and, accordingly, only slightly lower yields of enamides were obtained with bulky R_1 groups as shown in Table 1 (enamides **6a-e**). We have not mechanistic evidences yet, but it is probable that the enamides formation in the reaction between **1** and non aromatic aldimines could proceed through a stepwise (path a) or concerted (path b) addition of the corresponding Schiff bases to acetylketene **2**, as shown in Scheme 3. Oxazine formation should be prevented either by an intramolecular proton abstraction from dipolar intermediate 7 (path a) or an hydrogen shift in an "aza-Ene" transition state (path b), both leading to enamides.

Scheme 3



This simple method we describe for acetoacetylation of aldimines proves to be quite suitable. Thermolysis of dioxinone **1** gives acetylketene which reacts readily with imines without any added catalyst. Acetoacetic acid enamides were obtained in modest to good yields and in short reaction times under neutral conditions that ensure stability of products; no special precaution must be taken about reagents manipulation and also technical grade dioxinone (85% title) can be used; the workup procedure at the end of the reaction consists in simply evaporating the solvent. Moreover these data complete the study on the reactivity pattern of dioxinone **1** towards various imines from carbonyl compounds.

The obtained acetoacetyl enamides are really useful intermediates in the oxidative "*4-exo-trig*" radical ciclization leading to β-lactams that we already described.[8] By way of example enamide **6a** can be easily cyclized by reaction with $Mn(OAc)_3$ or CAN to give azetidinones **8** and **9** in 74 and 60 % yields respectively.[19]



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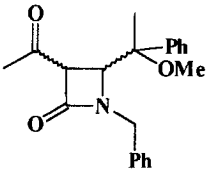

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17. A tipical experimental procedure is as follows: to a solution of imine (5 mmol) in 5 ml toluene was added 2,2,6-trimethyl-4H-1,3-dioxin-4-one **1** (5 mmol, 0.71 g) at room temperature. The reaction mixture was flushed with argon and immersed in an oil bath heated at 150 °C, and refluxed for 30 min; toluene was then evaporated and the residue poured on a silica gel column eluted with dichloromethane. Enamidic products were obtained as oils.
18. ^{1}H NMR data of products (200 MHz, $CDCl_3$): **6a**: 1.82 (3H, d, J= 1.4 Hz), 2.21 (3H, s), 3.50 (2H, s), 4.75 (2H, s), 6.24 (1H, q, J= 1.4 Hz), 7.2-7.4 (10H, m); **6b**: 0.91 (3H, t, J= 7.5 Hz), 1.60 (2H, sextuplet J=7.5 Hz), 2.00 (3H, d, J= 1.5 Hz), 2.20 (3H, s), 3.48 (2H, s), 3.50 (2H, t, J= 7.5 Hz), 6.33 (1H, q, J= 1.5 Hz), 7.3-7.5 (5H, m); **6c**: 1.14 (6H, d, J= 6.8 Hz), 2.00 (3H, d, J= 1.5 Hz), 2.19 (3H, s), 3.43 (2H, s), 4.89 (1H, heptuplet, J= 6.8 Hz), 6.24 (1H, q, J= 1.5 Hz), 7.3-7.5 (5H, m); **6d**: 1.0-2.0 (13H, m), 2.19 (3H, s), 3.42 (2H, s), 4.50 (1H, m), 6.23 (1H, br. s), 7.3-7.5 (5H, m); **6e**: 1.44 (9H, s), 2.00 (3H, d, J= 1.5 Hz), 2.15 (3H, s), 3.30 (1H, d, J= 15.9 Hz), 3.50 (1H, d, J= 15.9 Hz), 6.27 (1H, q, J= 1.5 Hz), 7.1-7.5 (5H, m); **6f**: 2.18 (3H, s), 3.60 (2H, s), 4.81 (2H, s), 6.42 (1H, d, J= 16 Hz), 6.76 (1H, d, J= 16 Hz); **6g**: 2.18 (2H, s), 3.09 (2H, s), 3.52 (2H, s), 4.70 (2H, s), 6.20 (1H, s), 7.0-7.5 (15H, m); **6h**: 1.52 (3H, s), 2.10 (3H, s), 3.07 (2H, s), 3.46 (2H, s), 4.50 (2H, s), 5.81 (1H, s), 7.0-7.4 (10H, m); **6i**: 1.26 (3H, d, J=7.2 Hz), 1.45 (3H, d, J= 1.4 Hz), 2.09 (3H, s), 3.06 (2H, s), 3.48 (2H, s), 5.55 (1H, q, J= 1.4 Hz), 5.95 (1H, q, J= 7.2 Hz), 7.0-7.4 (10H, m); **6j**: 1.41 (3H, d, J= 1.3 Hz), 2.81 (1H, dd, J_1= 16.0 Hz, J_2= 10.5 Hz), 2.90 (2H, s), 3.18 (1H, dd, J_1= 16.0 Hz, J_2= 5.6 Hz), 3.67 (3H, s), 5.01 (1H, dd, J_1= 10.5 Hz, J_2= 5.6 Hz), 5.62 (1H, t, J= 1.3 Hz), 7.0-7.4 (10H, m).
19. D'Annibale, A.; Resta, S.; Trogolo, C., unpublished results.

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