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An efficient procedure for the synthesis of formylacetic esters

Sofie Edvinsson, Susanne Johansson, Andreas Larsson *

Department of Chemistry, Umeå University, 901 87 Umeå, Sweden

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ABSTRACT

An efficient synthesis of formylacetic esters via ozonolysis of *trans*-β-hydromuconic esters followed by a solid-supported triphenylphosphine reduction has been developed. In addition, an extension toward formylacetic amides and a one-pot preparation of more stable intermediates which can be used for further transformations are also described.

There is a constant need for small reactive compounds, such as β-keto esters, in organic synthesis. Despite the fact that formylacetic esters are less stable than β-keto esters, they have found attention in the synthesis of a wide variety of heterocycles used in medicinal chemistry programs and in the total synthesis of natural products. These include, pyrimidones (**1**, **2**),[1] ring-fused azaindoles (**3**),[2] quinolones (**4**),[3] β-lactams (**5**),[4] coumarins (**6**),[5] and tetrahydropyrans (**7**)[6] (see Fig. 1).

Due to their instability, the synthesis of formylacetic esters is not as straightforward as for β-keto esters. One of the preferred synthetic methods is to allow an alcohol to react with formylketene, which is generated in situ from formyl Meldrum's acid.[7] This method is an extension of an earlier described procedure for the preparation of β-keto esters via acyl Meldrum's acids.[8] The synthesis described is elegant but suffers from the fact that the unstable esters have to be isolated through distillation. Additionally, the protocol does not easily allow further one-pot transformations into more stable intermediates, and the key intermediate in this synthesis, formyl Meldrum's acid, has to be prepared and used within a short period of time, altogether decreasing the practicality of the method and reducing the total yields of the formylacetic esters **10b–e** to a moderate 25–30% from commercial starting materials.[7] Herein, we report an efficient and convenient method for the synthesis and traceless isolation of formylacetic esters, based on the ozonolysis of *trans*-β-hydromuconic diesters, which also allows further one-pot syntheses to more advanced products in excellent yields.

Commercially available *trans*-β-hydromuconic acid (**8**) was esterified to give the corresponding carboxylic acid esters **9a–e** in high yields by a standard procedure (Table 1).[9] In the case of the *tert*-butyl ester **9d**, the general procedure employing triethylamine gave only traces of product. Satisfyingly, by exchanging the base to the more hindered amine, 2,4,6-collidine, the *tert*-butyl ester could be obtained in an 85% yield. The diamide **9f** was similarly prepared through a standard amide coupling procedure. In contrast to the formyl Meldrum's acid previously used for the preparation of formylacetic esters, all the esters prepared from *trans*-β-hydromuconic acid are stable and can be stored on the bench for extended periods of time without any noticeable decomposition.

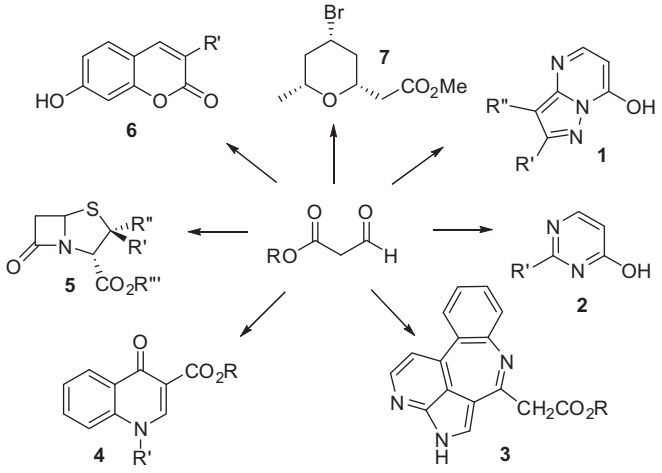

Figure 1. Examples of the utilization of formylacetic esters for the synthesis of various heterocycles.

* Corresponding author. Tel.: +46 90 786 6818; fax: +46 90 7867655.
E-mail address: andreas.larsson@chem.umu.se (A. Larsson).

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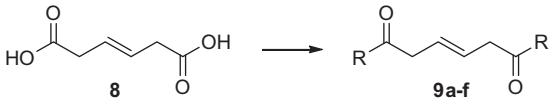
Table 1
Synthesis of *trans*-β-hydromuconic diesters and diamides **9a**–**f**[9]



Entry	R	Conditions	Yield (%)
a	MeO	PTSA (cat.), MeOH, rt, 18 h	95
b	EtO	(1) $(COCl)_2$ (4 equiv), C_6H_6, DMF (cat.), 35 °C, 2 h. (2) Et_3N (3 equiv), EtOH, rt, 1.5 h	93
c	*i*PrO	(1) $(COCl)_2$ (4 equiv), C_6H_6, DMF (cat.), 35 °C, 2 h. (2) Et_3N (3 equiv), *i*PrOH, rt, 2.5 h	75
d	*t*BuO	(1) $(COCl)_2$ (4 equiv), C_6H_6, DMF (cat.), 35 °C, 2 h. (2) 2,4,6-collidine (3 equiv), *t*BuOH, rt, 2.5 h	85
e	BnO	(1) $(COCl)_2$ (4 equiv), C_6H_6, DMF (cat.), 35 °C, 2 h. (2) Et_3N (3 equiv), BnOH, rt, 1.5 h	81
f	*i*PrNH	HATU (2.6 equiv), *i*PrNH$_2$ (2.5 equiv), 2,4,6-collidine (4 equiv), DMF, rt, 24 h	63

Initially, ozonolysis of the *trans*-β-hydromuconic esters **9b–e** was performed followed by applying standard reductive conditions (1.5 equiv of triphenylphosphine over 16 h), to reduce the ozonide, which had previously been shown in a few examples.[10] However, this method also required purification by Kügelrohr distillation, which led to the corresponding formylacetic esters **10b–e** in poor to moderate yields (Method A, Table 2).

The thermal instability of the formylacetic esters makes distillation less than optimal for their purification and resulted in the low isolated yields, especially for those with higher boiling points (compare **10b** and **10e** in Table 2). Still, an obvious advantage with this procedure, was the fact that 1 equiv of the starting material theoretically generates 2 equiv of the product which substantially increases the atom economy of the method. To avoid the purification step, we sought to use solid-supported triphenylphosphine in the reduction step, to facilitate easy and straightforward isolation through simple filtration.

Reducing the ozonide with triphenylphosphine in solution was accomplished overnight using 1.5 equiv of the reducing agent. Utilizing polystyrene-bound triphenylphosphine (PS-PPh$_2$) under identical conditions left a large amount of the ozonide unreacted. The reaction could be driven to completion by stirring for 48 h, although resulting in increased decomposition. The equivalents and reaction time were therefore optimized running the reaction in deuterated chloroform, and the decay of the ozonide was followed by NMR. Gratifyingly, employing 2 equiv of the reducing agent for 24 h, led to full conversion into the aldehyde without any detectable decomposition (see Method B, Table 2). This method could also be extended to the synthesis of the formylacetic amide **10f** (Table 2) in excellent yield.[11]

This method facilitates further manipulations in the same pot without isolation of the unstable formylacetic ester. This was exemplified by the one-pot synthesis of more stable equivalents of formylacetic esters,[12] the acetoxy- and silyloxy-derivatives **11a**,**b**, as well as the triflic acrylates **11c**,**d** (Table 3).

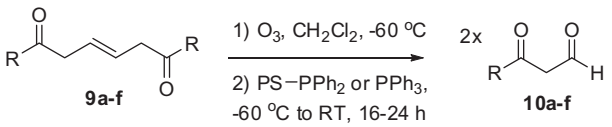
In the synthesis of the silanyloxy-, acetoxy-, and trifluoromethanesulfonyloxy derivatives **11a–c**, the formylacetic esters were carefully concentrated and quickly redissolved in THF. Next, a lithium enolate was generated by the addition of LDA, followed by quenching with either a silylating (TBSCl), acetylating (Ac_2O), or a triflating agent (Tf_2O). The stereoselectivity was moderate when the reaction was conducted at −78 °C giving an *E*:*Z* ratio of 2:1 (see entries **11a** and **b**). In contrast, running the reaction at −40 °C gave predominately a *Z* configuration (*E*:*Z* ratio 1:6, see entry **11c**).[13] Gratifyingly, this stereoselectivity could be altered in preference to the *E*-isomer (100:0) by running the reaction in dichloromethane and directly adding DBU in situ at −40 °C, followed by triflic anhydride (entry **11d**).[14]

Compounds **11c**,**d** were further transformed using standard palladium-catalyzed cross-coupling reactions, as exemplified by a Stille coupling (Scheme 1). The *Z*-isomer of the enol triflate **11c** was successfully coupled with retention of stereochemistry in the synthesis of alkyne acrylate **12** in good yield. Hence, they represent alternative intermediates in place of 3-iodoacrylates and phosphonoacetates, the two of the reactants previously used for the synthesis of conjugated acrylates, through copper-mediated[15] or Sonogashira couplings[16] and Horner–Wadsworth–Emmons reactions,[17] respectively.

4-Unsubstituted bicyclic β-lactams are found in a variety of β-lactamase inhibitors such as sulbactam,[18] tazobactam,[19] clavulanic acid,[20] and analogues thereof. To display further the applicability of the method developed, an advanced intermediate of the 6-unsubstituted penam **14** was synthesized. Di-*tert*-butyl hydromuconic ester (**9d**) was transformed into **10d** using Method B (Table 2), then filtered, and mixed with the methyl ester of D-penicillamine[21] to afford thiazolidine **13** in excellent yield (Scheme 2). From **13**, the penam **14** could be easily prepared by selective deprotection of the *tert*-butyl ester and subsequent lactamization.[4b]

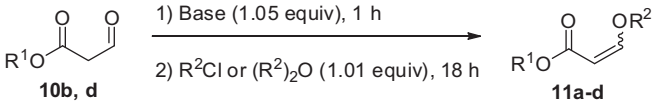
In conclusion, we have presented a method, based upon olefin cleavage with ozone, for the synthesis of formylacetic esters. By

Table 2
Synthesis of formylacetic esters and amides **10a**–**f**[11]



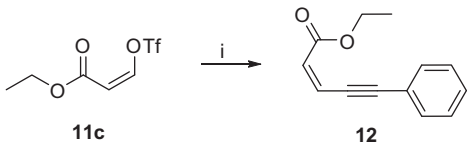
Entry	R	Reduction conditions	Yield (%) Method A	Yield (%) Method B
a	MeO	Method B: 2.0 equiv PS-PPh$_2$, −60 °C to rt, 24 h	—	90
b	EtO	Method A: 1.5 equiv PPh$_3$, −60 °C to rt, 16 h or Method B	65	95
c	*i*PrO	Method A or B	63	Quant
d	*t*BuO	Method A or B	46	Quant
e	BnO	Method A or B	24	Quant
f	*i*PrNH	Method B	—	Quant

Table 3
Derivatization of formylacetic esters

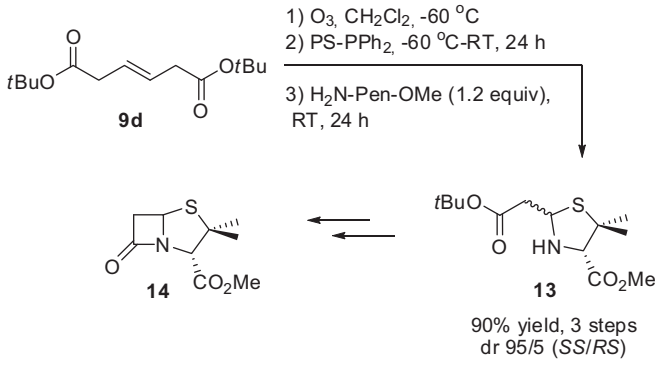


Entry	R^1	R^2	Conditions	*E*/*Z*	Yield (%)
a	*t*Bu	Ac	(1) LDA, THF, −78 °C (2) Ac_2O,−78 °C to rt	2/1	68[a]
b	*t*Bu	TBS	(1) LDA, THF, −78 °C (2) TBSCl,−78 °C to rt	2/1	64[a]
c	Et	Tf	(1) LDA, THF, −40 °C (2) Tf_2O,−40 °C to rt	1/6	50[a]
d	Et	Tf	(1) DBU, CH_2Cl_2, −40 °C (2) Tf_2O,−78 °C to rt	100/0	61[a]

[a] The enolic derivatives are volatile.



Scheme 1. Reagents and conditions: (i) tri-*n*-butyl(phenylethynyl)tin, LiCl, $Pd(Ph_3)_2Cl_2$, 2,6-di-*tert*-4-methylphenol, 1,4-dioxane, reflux, 4 h, 78%.



Scheme 2. Synthesis of penam **14**.

using solid-supported triphenylphosphine as the reducing agent, no distillation was needed rendering a high yielding and practical method. The procedure was also shown to be easily extended to include the formation of formylacetic amides. In addition, a one-pot in situ 'trapping' of these reactive intermediates gave the more stable derivatives, silyl enol esters and enol triflates: with excellent control over the stereochemistry. Finally, the convenience and efficiency of this method was further demonstrated by the synthesis of a penam intermediate. It is envisaged that this methodology might be extended with the direct conversion of the unstable intermediates into a number of different products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.021.

References and notes

1. (a) Mylari, B. L.; Oates, P. J.; Beebe, D. A.; Brackett, N. S.; Coutcher, J. B.; Dina, M. S.; Zembrowski, W. J. *J. Med. Chem.* **2001**, *44*, 2695–2700; (b) Gudmundsson, K. S.; Johns, B. A.; Weatherhead, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5689–5692.
2. Wang, T. S.; Ledeboer, M. W.; Duffy, J. P.; Pierce, A. C.; Zuccola, H. J.; Block, E.; Shlyakter, D.; Hogan, J. K.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 153–156.
3. Hendricks, R. T.; Fell, J. B.; Blake, J. F.; Fischer, J. P.; Robinson, J. E.; Spencer, S. R.; Stengel, P. J.; Bernacki, A. L.; Leveque, V. J. P.; Le Pogam, S.; Rajyaguru, S.; Najera, I.; Josey, J. A.; Harris, J. R.; Swallow, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3637–3641.
4. (a) Wolfe, S.; Sterzycki, R. Z. *Can. J. Chem.* **1987**, *65*, 26–30; (b) Chiba, T.; Sakaki, J.; Kobayashi, S.; Furuya, T.; Inukai, N.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 877–882.
5. Harada, K.; Kubo, H.; Tomigahara, Y.; Nishioka, K.; Takahashi, J.; Momose, M.; Inoue, S.; Kojima, A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 272–275.
6. Zhou, H.; Loh, T. P. *Tetrahedron Lett.* **2009**, *50*, 4368–4371.
7. Sato, M.; Naoki, Y.; Katagiri, N.; Watanabe, H.; Kaneko, C. *Synthesis* **1986**, *8*, 672–674.
8. Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087–2088.
9. *General procedure for the synthesis of diesters* ***9***: A suspension of 0.29 g (2.0 mmol) of trans-3-hexenedioic acid (**8**) in 3 mL of benzene was stirred at room temperature while 1.01 g (8.0 mmol) of $(COCl)_2$ and 1 drop of DMF were added. The resulting mixture was stirred at about 30–35 °C until the evolution of hydrogen chloride ceased (~2 h). The resulting clear orange solution was concentrated under reduced pressure, diluted with CH_2Cl_2, and concentrated under reduced pressure (two repeated sequences), to give the crude acid chloride as a dark red liquid: ^1H NMR (360 MHz, $CDCl_3$) δ 5.77 (m, 2H), 3.75 (dd, 4H, J = 15.4, 2.3 Hz). The resulting product was used immediately in the next step where it was added at room temperature over 30 min to a stirred solution of 607 mg (6.0 mmol) of Et_3N in 10 mL of alcohol. The mixture was stirred for 1 h before being diluted with 20 mL of Et_2O. The solution was sequentially washed with H_2O, 1 M HCl, $NaHCO_3$ (sat), and H_2O. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (heptane/EtOAc) to give the diesters (75–93% yield from **8**).
10. (a) Boisbrun, M.; Jeannin, L.; Toupet, L.; Laronze, J. Y. *Eur. J. Org. Chem.* **2000**, 3051–3057; (b) Chio, F. K.; Warne, J.; Gough, D.; Penny, M.; Green, S.; Coles, S. J.; Hursthouse, M. B.; Jones, P.; Hassall, L.; McGuire, T. M.; Dobbs, A. P. *Tetrahedron* **2011**, *67*, 5107–5124.
11. *General procedure for the synthesis of formylacetic esters/amide* ***10*** *(Method B)*: A stirred solution of diester/diamide **9** (0.4 mmol) in 8 mL of CH_2Cl_2 at −60 °C was treated with O_3 until it had a persistent blue colour. The mixture was then purged with nitrogen to remove excess O_3 (until colourless) and 0.8 mmol of solid supported triphenylphoshpine (1.6–3.2 mmol/g) was added before the mixture was allowed to warm to room temperature with stirring for 24 h. The solution was filtered and concentrated under reduced pressure to give the pure formylacetic esters/amide **10** (90–100% yield).
12. Fohlisch, B.; Giering, W. *Synthesis* **1980**, 231–232.
13. The isomers were easily separated by flash chromatography on a silica column.
14. Attempts with weaker amine bases, e.g. Et_3N, gave less selectivity.
15. Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441–1444.
16. (a) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631–633; (b) Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558–1561.
17. Dixon, D. J.; Lucas, A. C. *Synlett* **2004**, 1092–1094.
18. English, A. R.; Retsema, J. A.; Girard, A. E.; Lynch, J. E.; Barth, W. E. *Antimicrob. Agents Chemother.* **1978**, *14*, 414–419.
19. Aronoff, S. C.; Jacobs, M. R.; Johenning, S.; Yamabe, S. *Antimicrob. Agents Chemother.* **1984**, *26*, 580–582.
20. Howarth, T. T.; Brown, A. G.; King, T. J. *J. Chem. Soc., Chem. Commun.* **1976**, 266–267.
21. Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3784–3786.