ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2018; 4(3): 505-506
www.allresearchjournal.com
Received: 19-01-2018
Accepted: 21-02-2018

Amrita Raj
Research Scholar, Department of Chemistry, L.N.M.U., Darbhanga, Bihar, India

Correspondence
Amrita Raj
Research Scholar, Department of Chemistry, L.N.M.U., Darbhanga, Bihar, India

New approach of the synthesis of β-ketoesters

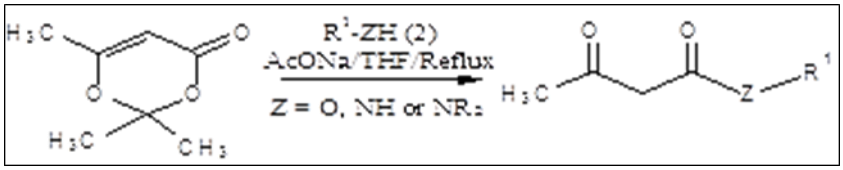
Amrita Raj

Abstract
In the presence of sodium acetate, the reaction between 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and secondary or tertiary alcohols (including chiral ones) or primary or secondary amines could be carried out in refluxing tetrahydrofuran, under much milder conditions than those described in the literature. In these new conditions, side products normally observed using the traditional protocol were avoided and β-keto esters were normally obtained in quantitative yields.

Keywords: Acetoacetylation, chiral auxiliaries, dicarbonyl compounds, esters, amides

Introduction

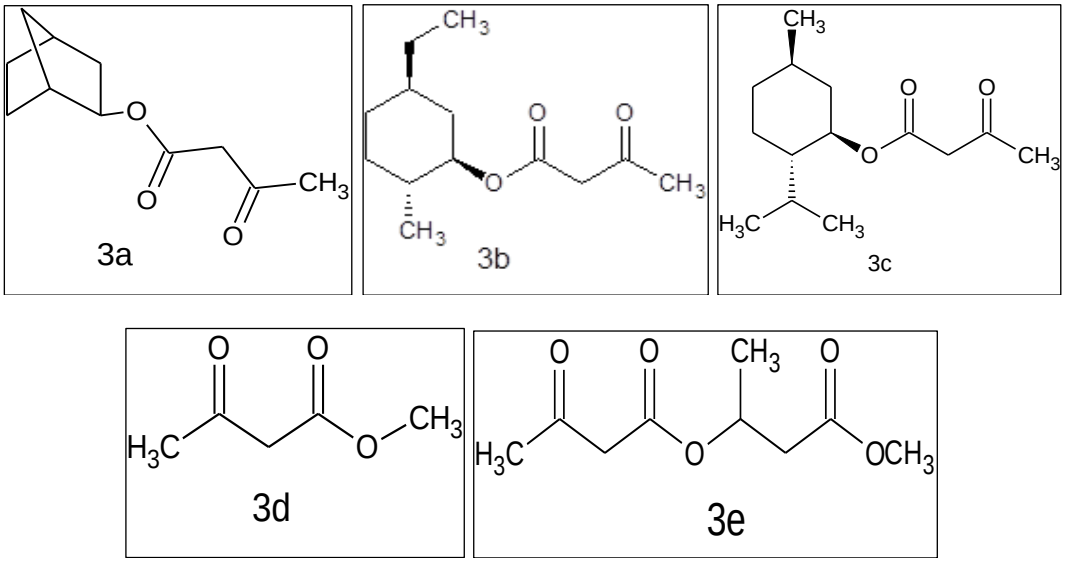
Scheme



The β-Dicarbonyl compounds are recognized as very important building blocks in organic synthesis and are used for the construction of a variety of biologically relevant molecules [1-3]. They are also excellent starting materials for the synthesis of heterocyclic compounds such as dihydropyridines (Hantzsch), pyrroles (Knorr), dihydropyrimidinones (Biginelli), indoles (Nenitzescu), quinolines (Combes, Conrad-Limpach, Friedländer, Knorr), often through multi component strategies [4]. Furthermore, β-dicarbonyl compounds can also be used for the construction of carbocycles by means of C-C bond formation reactions [5-7]. Among these compounds, β-keto esters are particularly interesting because they may contain suitable chiral auxiliary groups and hence, be used to carry out asymmetric transformations [8]. The most straightforward synthetic entry into chiral β-keto esters involves either transesterification of ethyl or methyl acetoacetate or treatment of chiral alcohols with acetoacetylating reagents. Transesterification is an equilibrium process and an acidic or basic catalyst is required to promote the reaction, which, nevertheless, often gives poor yields. A number of modified procedures have been developed that employ Lewis acids to avoid the limitations of classical conditions[5]. Nevertheless, as shown by our own experience, many of these new methods have the drawback of poor reproducibility. The alternative method for the synthesis of chiral b-keto esters involves the reaction between chiral alcohols and acetoacetylating reagents, the first of which was diketene [6]. Although this reagent gives good yields, a number of problems are associated with its use, such as high reactivity and moisture sensitivity, coupled to its lachrymatory and toxic character. These drawbacks prompted Clemens and Hyatt to develop a convenient alternative to diketene, namely 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1), a 1:1 acetone-diketene adduct [7]. Pyrolysis of compound 1 at 150 °C in high-boiling solvents gives acetylketene through a retro-hetero-Diels–Alder reaction and this intermediate can be trapped by nucleophiles to give their acetoacetylation products. In addition to the obvious disadvantages of the requirement for high temperatures, such as the impossibility of applying the reaction to thermally unstable substrates, at these temperatures acetylketene undergoes dimerization in a [4+2] fashion or reacts with acetone liberated during the reaction leading to side products that prevent complete conversion [7-13]. While derivatives of 1 with

substituents other than methyl are known [10], they are not commercially available and their use is normally limited to specialized applications.

In the course of our research on the application of β-dicarbonyl compounds for the synthesis of heterocycles and carbocycles using multicomponent reactions [3, 11-17], I needed to prepare chiral β-keto esters and found that currently existing methods were not wholly satisfactory. We report now the development of a modified synthetic procedure for the practical synthesis of acetoacetates 3 from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1) and alcohols, including chiral alcohols, or primary or secondary amines under mild conditions that avoid side reactions and give essentially quantitative yields.



Initially, I carried out the reaction between 1 and borneol, a readily available, sterically hindered secondary chiral alcohol, in tetrahydrofuran under reflux. After 24hours, we observed only 58% conversion, which made it obvious that the reaction needed high temperatures or a catalyst to promote acetylketene formation. However, when we carried out the reaction in the presence of one equivalent of sodium acetate, the reaction was completed in 30 hours with a quantitative yield of 3a. The use of a higher excess of 1 did not reduce the reaction time significantly (entries 3 and 4), and the use of potassium carbonate instead of sodium acetate had no effect upon the reaction. It should also be mentioned that the reactionmust be carried out in concentrated solutions (ca. 1.5 M) and was slow in more dilute reaction mixtures. Subsequently, we applied our optimal conditions to the synthesis of three additional chiral β-keto esters 3b-d from other chiral alcohols often used as chiral auxiliaries, namely menthol. phenylmenthol and cholesterol. In all cases, the yields were quantitative and it is worth mentioning that the less hindered cholesterol needed a reaction time of only 12 hours. Importantly, the reaction could be carried out on a scale of up to 15 mmol of the starting materials without any decrease in the yield. In further experiments, involvingsimpler starting alcohols, I proved the feasibility of using the alcohol itself as the reaction medium), and also of employing tertiary alcohols always giving the products 3e in quantitative yields.

References

1. Benetti S, Romagnoli R, De Risi C, Spalluto G, Zanirato V. Chem. Rev 1995;95:10-65.
2. Simon C, Constantieux T, Rodriguez J. Eur. J Org. Chem 2004, 49-57.
3. Ducatti DRB, Massi A, Noseda MD, Duarte MER, Dondoni A. Org. Biomol. Chem 2009; 7:19-80.
4. Debache A, Boulcina R, Belfaitah A, Rhouati S, Carboni B. Synlett 2008, 509.
5. Chitra S, Pandiarajan K. Tetrahedron Lett 2009;50:22-22.
6. Singh OM, Devi NSJ. Org. Chem 2009;74:31-41.
7. Velezheva VS, Sokolov AI, Kornienko AG, Lyssenko KA, Nelyubina YV, Godovikov IA *et al*. Tetrahedron Lett 2008;49:7106.
8. Wang HM, Hou RS, Cheng HT, Chen LC. Heterocycles. 2009; 78:487.
9. Thomae D, Perspicace E, Hesse S, Kirsch G, Seck P. Tetrahedron 2008;64:9309.
10. Sridharan V, Menéndez JC. Org. Lett 2008; 10:43-03.
11. Xu HW, Li GY, Wong MK, Che CM. Org. Lett 2005;7:53-49.
12. Frantz R, Hintermann L, Perseghini M, Broggini D, Togni A. Org. Lett 2003; 5:1709.
13. Myers AG, Tom NJ, Fraley ME, Cohen SB, Madar DJ. J Am. Chem. Soc 1997; 119:60-72.
14. Gilbert JC, Kelly TA. J Org. Chem 1988; 53:449.
15. Chavan SP, Kale RR, Shivashankar K, Chandake SI, Benjamin SB. Synthesis 2003, 26-95.
16. Ribeiro RS, De Souza ROMA, Vasconcellos MLAA, Oliveira BL, Ferreira LC, Aguiar LCS. Synthesis 2007, 61.
17. Kondaiah GCM, Reddy LA, Babu KS, Gurav VM, Huge KG, Bandichhor R *et al*. Tetrahedron Lett 2008; 49:106.