

Synthesis of the Furan Nucleus Promoted by Ytterbium Triflate

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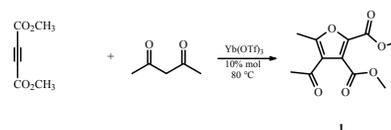
An efficient synthesis of differently substituted furans from acetylene dicarboxylates and β -dicarbonyl compounds is described. The furan nucleus was built by means of an $\text{Yb}(\text{OTf})_3$ catalyzed cycloaddition reaction yielding desired adducts in 91% - 98% yield.

Keywords: Alkynoates, Cycloadditions, Furan, Heterogeneous catalysis, Lanthanides, Ytterbium triflate.

The set-up of simple methodology to have access to useful chemicals is one of the most important tasks in organic synthesis. In this regard, furans are valuable and important products being components of secondary metabolites of plant, bacterial, and fungal origin, of pharmaceuticals [1-5], and organic materials [6-7]. Thus, the synthesis of furans represents an important and valuable task in organic chemistry and still represents a field of research of current and growing interest. Several methods for the synthesis of the furan nucleus have been reported in the literature and among these several "classic" examples in the history of organic chemistry can be cited. The Paal-Knorr [2-5] and the Feist-Benary [8] reactions, straightforward synthesis of the title compounds, are two of these processes. Both reactions can be promoted by the use of mineral acids, organic bases, and Lewis acids. In this latter context several transition metals including Rh(I), Ag(I), Au (III), and Pd (0/II) have been employed to build the furan nucleus starting from 1,2-allenylketones [9-10]. Another strategy makes use of a combination of CuI and SnCl_2 and alkynoates and β -dicarbonyl compounds as substrates [11-12]. Unfortunately, some of the reported methodologies has several disadvantages like non-mild experimental conditions, yields not sufficiently good, work-up procedures difficult to handle, low selectivity, co-occurrence of side reactions, and need of column chromatographic procedures.

In the last thirty years, triflates of rare earth metals have been discovered to be unconventional Lewis acids being reusable catalysts able to tolerate water as solvents. Moreover, they can efficiently promote carbon-carbon and carbon-heteroatom bond formations in satisfactory yields [13]. During our studies on lanthanide triflates as catalysts, we have recently observed that such metals, in particular $\text{La}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$, can effectively promote these processes in the frame of a green chemical approach [14-15]. As a continuation of our investigations to develop mild protocols for the synthesis of useful building blocks and/or biologically active products using lanthanides as catalysts and water as the solvent or solvent-free conditions, we wish to describe in this manuscript that furan derivatives can be effectively synthesized under the catalysis of $\text{Yb}(\text{OTf})_3$ hydrate in good yields starting from acetylene dicarboxylates and β -dicarbonyl compounds (Scheme 1).

In a first series of experiments, to dimethyl acetylene dicarboxylate (1 eq.) and 2,4-pentandione were added 10% mol $\text{Yb}(\text{OTf})_3$ hydrate. The resulting reaction mixture was vigorously stirred at 80°C for 1 h. After the addition of 1M NaOH to precipitate Yb^{+3} as



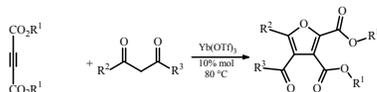
Scheme 1

its hydroxide, followed by filtration and extraction with Et_2O , the desired adduct, dimethyl-4-acetyl-5-methylfuran-2,3-dicarboxylate (entry 1), was obtained in 85% yield. Hydrolysis of the ester functions in the obtained product was recorded to be very limited and was virtually undetectable. To characterize better the scopes and limitations of our process, other slightly structurally different alkynoates (e.g. diethyl acetylene dicarboxylate) and β -dicarbonyl compounds were employed as substrates. The results of other reactions are reported in Table 1.

From data recorded it is evident that β -dicarbonyl compounds employed as substrates (e.g. β -diketones bearing alkyl or aryl residues linked to the carbonyl group and β -ketoesters) reacted similarly providing the desired products in 70% to 85% yields. For a comparison with the already reported processes in the same field, our methodology avoids the use of excess strong mineral or Lewis acids, as well as long reaction times. The catalyst was always recovered by precipitation as $\text{Yb}(\text{OH})_3$, filtered, and transformed into the triflate salt, as already described [16]. Recycled in this way, the catalyst has been reused several times without any significant loss of activity. For example, the product of entry 1 was obtained in 73%, 69%, 74%, and 78% after repetition of four additional reactions. The same reaction was also performed by using other metal triflates from the lanthanide series (e.g. La, Eu, Gd), but the results were not as good as those obtained with $\text{Yb}(\text{OTf})_3$ in terms of yields. The observed discrepancy in the catalytic efficiency may be due to the feature of Yb^{+3} as the "hardest" cation in the lanthanide series and thus the most oxophilic, due to its smaller ionic radius [17].

For what concerns the mechanism of this reaction, it may be hypothesized that Yb^{+3} coordinates both the alkynoate and the β -dicarbonyl compound thus enhancing each other's reactivity towards the addition, leading to the formation of the furan ring.

As a conclusion, in this manuscript we have shown that either dimethyl- or diethyl acetylene dicarboxylates and differently

Table 1: Yb(OTf)₃ catalysed synthesis of furan derivatives.

| Entry | Alkynoate | Substrate | Product | Yield % ^a |
|-------|---------------------|---|---------|----------------------|
| 1 | R ¹ = Me | R ² = R ³ = Me | | 95 |
| 2 | R ¹ = Me | R ² = Me, R ³ = OEt | | 91 |
| 3 | R ¹ = Me | R ² = Me, R ³ = Et | | 98 |
| 4 | R ¹ = Me | R ² = R ³ = Ph | | 92 |
| 5 | R ¹ = Et | R ² = R ³ = Me | | 94 |
| 6 | R ¹ = Et | R ² = Me, R ³ = OEt | | 95 |
| 7 | R ¹ = Et | R ² = Me, R ³ = Et | | 92 |
| 8 | R ¹ = Et | R ² = R ³ = Ph | | 91 |

substituted aromatic and aliphatic β-diketones and β-ketoesters undergo a condensation reaction under the catalysis of Yb(OTf)₃ hydrate providing substituted furans. An easy workup procedure, mild experimental conditions, and good to excellent yields render our methodology a valid and alternative contribution to the already described processes in the field of furan synthesis. Finally, the reported protocol represents a practical application of solvent-free reactions. Further investigations to characterize better the scope and limitations of the presented methodology are ongoing in our laboratories and will be reported in due course.

Experimental

General: All reagents and substrates were purchased from Aldrich Chemical Co. and used without further purification. All solvents were of analytical grade. All extracts were dried over anhydrous Na₂SO₄. ¹H and ¹³C NMR spectra were recorded on a Bruker AC 200 (¹H NMR, 200 MHz; ¹³C NMR, 50.32 MHz). CDCl₃ was used as the solvent and tetramethylsilane as an internal standard. Chemical shifts are reported in δ (ppm). Reactions were monitored by TLC using Merck silica gel F₂₅₄ plates and visualization of TLC spots was achieved with a freshly prepared 7% ethanolic phosphomolybdic acid solution. Melting points were measured on a Büchi apparatus. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer. The purity of the intermediates and the final products was confirmed by combustion analysis.

Synthesis of furan derivatives. General procedure: Yb(OTf)₃ hydrate (0.1 mmol) was added to a suspension of alkynoate (1.0 mmol) and β-dicarbonyl compound (1.0 mmol). The resulting mixture was well stirred for 1 h at 80°C. Then a few drops of NaOH 1N were added, and the white precipitate so formed was filtered under vacuum. The filtrate was extracted with Et₂O (5 x 2 mL) and the solvent evaporated to dryness providing the desired adduct without the need of further purification.

Dimethyl 4-acetyl-5-methylfuran-2,3-dicarboxylate (entry 1): Analytical data were in full agreement with those already reported in the literature for the same compound [18].

C₁₁H₁₂O₆ calcd. C 55.00, H 5.04, O 39.96; found C 54.94, H 5.01, O 39.92.

4-Ethyl 2,3-dimethyl 5-methylfuran-2,3,4-tricarboxylate (entry 2): Analytical data were in full agreement with those already reported in the literature for the same compound [18].

C₁₂H₁₄O₇ calcd. C 53.34, H 5.22, O 41.44; found C 53.30, H 5.17, O 41.40.

Dimethyl 5-methyl-4-propionylfuran-2,3-dicarboxylate (entry 3): Yellow solid.

MP: 101-102°C.

¹H NMR (200 MHz, CDCl₃): 3.89 (s, 3H), 3.52 (s, 3H), 2.82 (q, 2H, *J*=7.4 Hz), 2.65 (s, 3H), 1.16 (t, 3H, *J*=7.4 Hz).

¹³C NMR (200 MHz, CDCl₃; Me₄Si) δ: 197.4, 162.7, 161.2, 157.8, 154.8, 124.4, 119.1, 51.5, 51.4, 35.7, 13.3, 8.9.

MS: *m/z* (%): 254 (100) [M⁺], 55, 67, 82, 96, 110, 123, 138, 149, 163, 181, 225, 241.

C₁₃H₁₆O₆ calcd. C 58.20, H 6.01, O 35.78; found C 57.98, H 6.23, O 35.79.

Dimethyl 4-benzoyl-5-phenylfuran-2,3-dicarboxylate (entry 4): Analytical data were in full agreement with those already reported in the literature for the same compound [18].

C₂₁H₁₆O₆ calcd. C 69.23, H 4.43, O 26.35; found C 69.18, H 4.37, O 26.31.

Diethyl 4-acetyl-5-methylfuran-2,3-dicarboxylate (entry 5): Analytical data were in full agreement with those already reported in the literature for the same compound [18].

C₁₃H₁₆O₆ calcd. C 58.20, H 6.01, O 35.78; found C 58.16, H 6.07, O 35.71.

Triethyl 5-methylfuran-2,3,4-tricarboxylate (entry 6): Analytical data were in full agreement with those already reported in the literature for the same compound [18].

C₁₄H₁₈O₇ calcd. C 56.37, H 6.08, O 37.55; found C 56.39, H 6.00, O 37.52.

Diethyl 5-methyl-4-propionylfuran-2,3-dicarboxylate (entry 7): Yellow solid.

MP: 101-102°C.

¹H NMR (200 MHz, CDCl₃; Me₄Si) δ: 4.36 (q, 2H, *J*=7.4 Hz), 4.33 (q, 2H, *J*=7.1 Hz), 2.81 (q, 2H, *J*=7.4 Hz), 2.64 (s, 3H), 1.17 (t, 3H, *J*=7.4 Hz).

¹³C NMR (200 MHz, CDCl₃; Me₄Si) δ: 197.8, 165.0, 162.2, 159.2, 155.7, 124.8, 118.4, 62.4, 61.7, 35.7, 14.1, 14.0, 13.3, 8.8.

MS: *m/z* (%): 281 (100) [M⁺], 55, 67, 83, 97, 111, 124, 137, 165, 195, 209, 221, 237, 253, 268.

C₁₄H₁₈O₆ calcd. C 59.57, H 6.43, O 34.01; found C 59.35, H 6.76, O 34.11.

Diethyl 4-benzoyl-5-phenylfuran-2,3-dicarboxylate (entry 8): C₂₃H₂₀O₆ calcd. C 70.40, H 5.14, O 24.46; found C 70.38, H 5.08, O 24.41. Analytical data were in full agreement with those already reported in the literature for the same compound [18].

References

- [1] Brown RCD. (2005) Developments in furan synthesis. *Angewandte Chemie International Edition*, **44**, 850-853.
- [2] Cacchi S. (1999) Heterocycles via cyclization of alkynes promoted by organopalladium complexes. *Journal of Organometallic Chemistry*, **576**, 42-64.
- [3] Hou XL, Cheung HY, Hon TY, Kwan PL, Lo TH, Tong SY, Wong HNC. (1998) Regioselective syntheses of substituted furans. *Tetrahedron*, **54**, 1955-2020.
- [4] Keay BA. (1999) Synthesis of multi-substituted furan rings: the role of silicon. *Chemical Society Reviews*, **28**, 209-215.
- [5] Lipshutz BH. (1986) Five-membered heteroaromatic rings as intermediates in organic synthesis. *Chemical Reviews*, **86**, 795-819.
- [6] Guillard J, Meth-Cohn O, Rees CW, White AJP, Williams DJ. (2002) Direct conversion of macrocyclic furans into macrocyclic isothiazoles. *Chemical Communications*, 232-233.
- [7] Lee CF, Yang LM, Hwu TY, Feng AS, Tseng JC, Luh TY. (2000) One-pot synthesis of substituted furans and pyrroles from propargylic dithioacetals. New annulation route to highly photoluminescent oligoaryls. *Journal of the American Chemical Society*, **122**, 4992-4993.
- [8] Minetto G, Raveglia LF, Sega A, Taddei M. (2005) Microwave-assisted Paal-Knorr reaction – three-step regiocontrolled synthesis of polysubstituted furans, pyrroles and thiophenes. *European Journal of Organic Chemistry*, 5277-5288.
- [9] Ila H, Baron O, Wagner AJ, Knochel P. (2006) Functionalized magnesium organometallics as versatile intermediates for the synthesis of polyfunctional heterocycles. *Chemical Communications*, 583-593.
- [10] Sromek AW, Rubina M, Gevorgyan V. (2005) 1,2-Halogen migration in haloallenyl ketones: regiodivergent synthesis of halofurans. *Journal of the American Chemical Society*, **122**, 10500-10501.
- [11] Liu W, Jiang H, Zhang M, Qi C. (2010) Combining asymmetric catalysis with natural product functionalization through enantioselective α -fluorination. *Journal of Organic Chemistry*, **75**, 966-968.
- [12] Ma S, Zhang J, Lu L. (2003) Pd⁰-Catalyzed coupling cyclization reaction of aryl or alkenyl halides with 1,2-allenyl ketones: scope and mechanism. An efficient assembly of 2,3,4-, 2,3,5-tri- and 2,3,4,5-tetrasubstituted furans. *Chemistry European Journal*, **9**, 2447-2456.
- [13] Kobayashi S, Sugiura M, Kitagawa H, Lam WL. (2009) Rare-earth metal triflates in organic synthesis. *Chemical Reviews*, **102**, 2227-2302.
- [14] Fiorito S, Genovese S, Taddeo VA, Epifano F. (2015) Microwave-assisted synthesis of coumarin-3-carboxylic acids under ytterbium triflate catalysis. *Tetrahedron Letters*, **56**, 2434-2436.
- [15] Genovese S, Fiorito S, Specchiulli MC, Taddeo VA, Epifano F. (2015) Microwave-assisted synthesis of xanthenes promoted by ytterbium triflate. *Tetrahedron Letters*, **56**, 847-850.
- [16] Fieser M. (1989) *Reagents for Organic Synthesis*, Wiley-Interscience, New York, **14**, 188.
- [17] Pitzer KS. (1979) Relativistic effects on chemical properties. *Accounts on Chemical Research*, **12**, 271-275.
- [18] Yan R, Huang J, Luo J, Wen P, Huang G, Liang Y. (2010) Copper(I)-catalyzed synthesis of polysubstituted furans from alkynoates and 1,3-dicarbonyl compounds in the presence of oxygen. *Synlett*, 1071-1074.