Chemo-differentiating MCRs based on α-ketoesters and terminal alkynoates. A homoaldol-based ABB′ system

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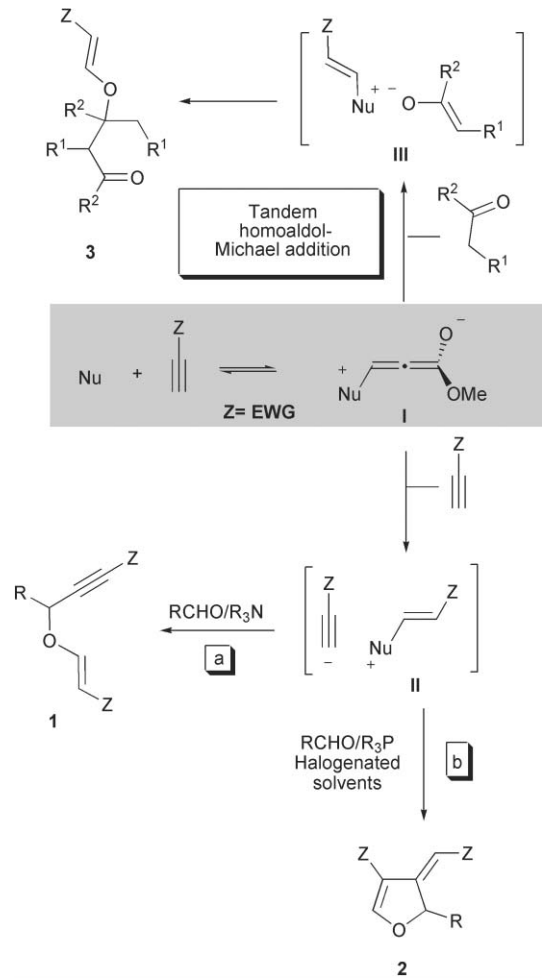
A novel ABB′ 3 component reaction (3-CR) system based on the organocatalyzed homoaldolic condensation of α-ketoesters in the presence of terminal conjugated alkynoates is described.

Multicomponent reactions (MCRs) constitute excellent manifolds for the generation of molecular complexity in an economical and atom-efficient manner.[1] They perform molecular construction by the generation of more than two chemical bonds per operation, with high convergence, easy structure-diversification and a broad chemical outcome. As a part of a research program aimed at the development of new diversity-oriented synthetic methodologies,[2] we have been involved in the design and development of novel bimolecular domino processes displaying some of the synthetic advantages associated with MCRs. Our general design concept relies on the development of chemical processes able to transform a degenerate set of chemical inputs into a final product whose structure incorporates each reactant several times and in the form of differentiated chemical functions or structural motifs (non-degenerate chemical output). The simplest case should be that represented by a 3-CR involving only two starting materials. We categorize this kind of domino process as ABB′ to highlight its bimolecular nature (A and B) and the dual role played by component B along the reaction pathway (B and B′).[4,5] In spite of the potential interest and synthetic value of these 3-CRs, the number of precedents in the literature is scarce.[6]

In this communication, we disclose a novel aldol-based ABB′ system comprising a chemo-differentiating MCR of α-ketoesters and terminal alkynoates catalyzed by tertiary amines. We have recently described a set of ABB′ systems based on a novel reactivity concept: the generation of a strong base by the action of a good nucleophile (Scheme 1).[3] Key to these systems is the catalytic generation of allenoate **I** by reaction of a nucleophile (catalyst) and a terminal alkynoate. In the presence of aldehydes, two domino reactions take place affording propargylic enol ethers **1** (path a, Scheme 1) or dihydrofuranes **2** (path b, Scheme 1) as a function of temperature, catalyst nature and solvent. We speculated that the use of aldehydes or ketones more acidic than the propiolate itself (pK_a = 18.8)[7] ought to inhibit these processes, triggering a new set of domino processes based on the formation of enolate **III** (Scheme 1). These new enolate-driven domino processes would generate γ-ketoenol ethers **3** *via* a catalytic cycle involving a tandem homoaldol condensation–Michael-addition pair of reactions. While the homoaldol condensation would allow the chemo-differentiation of two units of the carbonyl-containing starting material, the Michael-addition reaction would close the cycle by formation of product **3** and catalyst regeneration. The practical use of this chemo-differentiated processing would give rise to a novel and profitable homoaldol-based ABB′ 3-CR.

Preliminary experimental approaches to this conceptual system revealed a reactivity threshold for the carbonyl reactant. While simple and enolizable aldehydes were consistently incorporated into adducts type **1** or **2** (path a and b, Scheme 1), normal and enolizable ketones did not react under these conditions. α-Ketoesters display both higher reactivity and acidity than simple ketones while incorporating an added point of reactivity in



Scheme 1 Allenolate-driven domino processes.

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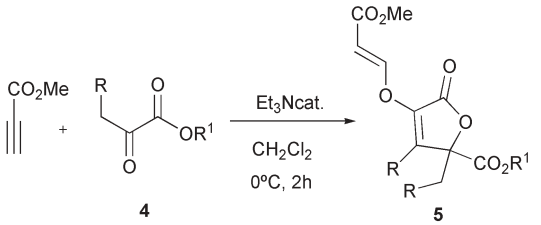
Table 1 ABB′ 3-CR of α-ketoesters and methyl propiolate catalyzed by triethylamine (20 mol%)[a]



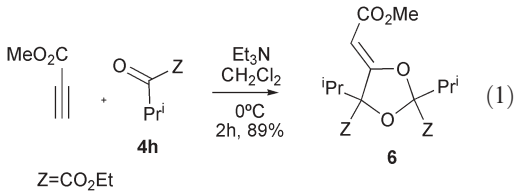
4 5

Entry	R	R^1	Product	Yield (%)[b]
1	H	Et	**5a**	81
2	Me	Me	**5b**	90
3	Et	Me	**5c**	80[c]
4	Et	Me	**5c**	90[d]
5	Heptyl	Et	**5d**	89[d]
6	$PhCH_2$	Et	**5e**	89
7	MeO_2CCH_2	Me	**5f**	85
8	MeO_2C	Me	**5g**	NR[e]

[a] α-Ketoester (2 eq.), methyl propiolate (1 eq.), Et_3N (0.2 eq.), CH_2Cl_2, 0 °C, 1 h. [b] Yield of isolated, analytically pure products. [c] 8% isolated yield of enol ether product obtained from the alkylation of enolate **III**. [d] Reaction conducted in THF. [e] No reaction.

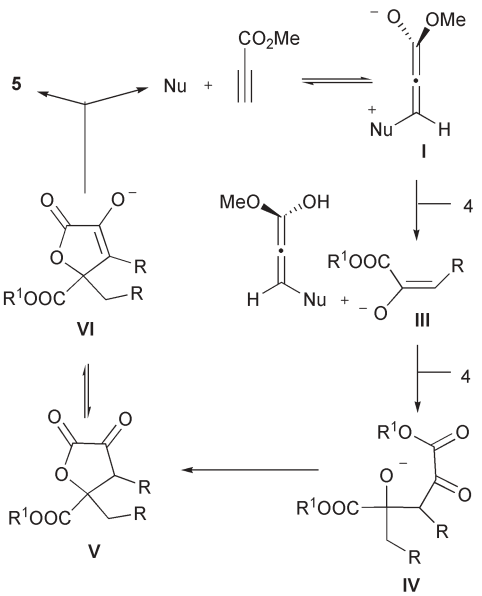
the form of an ester functionality. When methyl propiolate, ethyl 2-oxopropanoate (**4a**) and a catalytic amount of triethylamine (20 mol%) were mixed in dichloromethane at 0 °C, a clean and smooth reaction took place to afford the isotetronic acid derivative **5a**† in 81% yield (Table 1, entry 1). The product incorporated one unit of methyl propiolate (in the form of an α,β-alkenoate) and two units of the 2-oxopropanoate (in the form of the aldol-adduct), forming a fully-functionalized α,β-unsaturated γ-lactone core decorated with a diverse set of appended chemical functionalities (two alkyl chains, one conjugated enol ether and two carboxylic esters: one conjugated and the other non-conjugated). This reaction constitutes the first example of this novel ABB′ 3-CR, and it provides convenient and diversity-oriented access to this chemically and biologically important family of structural motifs.[8,9] Other aliphatic ketoesters behaved as suitable reactants for this process, generating the corresponding isotetronic acid derivatives **5a–f** in an excellent 85% average yield (Table 1, entries 1–7).

A limitation arises when the α-position bears an ester group (entry 8) or a substituent (eqn (1)).



(1)

A plausible mechanism is outlined in Scheme 2. The domino process is initiated by a fast formation of allenolate **I**, which triggers the catalytic cycle by generation of the ammonium enolate **III**.[10] Homoaldol reaction with another molecule of α-ketoester **4** affords the aldol-adduct **IV**.[11] A sequential lactonization–deprotonation reaction followed by a tandem Michael-addition–elimination on the β-ammonium acrylate counterion forms the isotetronic acid derivative **5** with catalyst (nucleophile) regeneration to restart the cycle. Lactonization of alkoxide **IV** liberates one



Scheme 2 Mechanistic proposal for the homoaldolic-based ABB′ 3-CR.

molecule of alcoholate, which is basic enough to deprotonate the highly acidic α-ketolactone **V**. Note that the ester group does not play the unique role of a keto-activating group; it is also utilized to generate the lactone ring. Enolates derived from β-substituted α-ketoesters (*i.e.* **4h**), although they are kinetically accessible, display a diminished reactivity toward the homoaldolic reaction and their sterically congested homoadducts present important kinetic inhibition toward the lactonization reaction. Under these conditions, an alkynylide-driven competitive and irreversible domino process begins to operate, funnelling the chemical transformation toward the formation of the 1,3-dioxolane derivatives **6** (eqn (1)).[12]

In summary, we have designed a novel ABB′ 3-CR system based on the organocatalyzed homoaldolic condensation of α-ketoesters in the presence of terminal conjugated alkynoates. This reaction generates polyfunctionalized isotetronic acid derivatives with atom-efficiency and easy chemical processing. The reaction network operates under the domino principle to construct an α,β-unsaturated γ-lactone ring, two C–O bonds and one C–C bond, with an exquisite and efficient utilization of all and every one of the different reactivities associated with the α-ketoester functionality (Fig. 1). The γ-lactone ring incorporates two units of the starting α-ketoester in a very differentiated manner and it is decorated with a diverse set of different appended chemical functionalities. Each appended functionality can be selective and

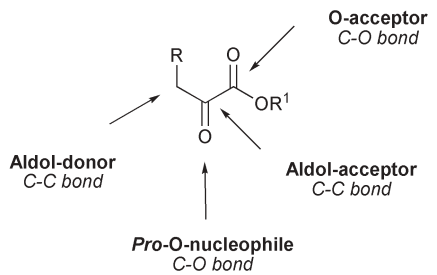


Fig. 1 Reactivity profile of the α-ketoester functionality.

productively utilized to modulate the biological activity and/or chemical reactivity of the isotetronic acid core.

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Notes and references

† General procedure: methyl propiolate (1.00 mmol) and ethyl 2-oxopropanoate (**4a**) (2.00 mmol) were dissolved in 2 mL of CH_2Cl_2 (or THF). After the mixture was cooled to 0 °C, triethylamine (0.2 mmol) was added and the reaction mixture was allowed to stir for 1–4 h. The solvent and excess reagents were then removed under reduced pressure. This was followed by isolation of the corresponding isotetronic product **5a** (81%) by flash column chromatography (silica gel, *n*-hexane : EtOAc 80 : 20 to 60 : 40). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.18 (t, 3H, J = 7.2 Hz), 1.65 (s, 3H), 3.62 (s, 3H), 4.13 (q, 2H, J = 7.2 Hz), 5.71 (d, 1H, J = 12.0 Hz), 6.67 (s, 1H), 7.57 (d, 1H, J = 12.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 13.8, 22.5, 51.5, 62.7, 82.5, 106.0, 124.7, 143.1, 155.0, 164.5, 166.0, 167.6. IR ($CHCl_3$, cm^{-1}) 1127.0, 1222.1, 1646.1, 1727.2, 1793.2, 3020.4. Anal. calc. for $C_{12}H_{14}O_7$: C, 53.33; H, 5.22. Found: C, 53.31; H, 5.2574. MS, *m/z* (relative intensities) 270 (M^+, 1.3), 227 (43), 197 (100), 166 (69), 127 (36), 121 (26), 96 (28), 85 (49), 59 (46).

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4 We have taken this notation from the pioneering work of Powell and Batey: D. A. Powell and R. A. Batey, *Org. Lett.*, 2002, **4**, 2913–2916.

5 It is a different scenario to those categorized as AB_2 or AB^2, in which the component B plays the same role twice along the whole process.

6 We are preparing a full account of these ABB′ systems with our own contributions and other synthetic examples found in our literature search. For selected examples see: (*a*) H. Neumann, A. J. von Wangelin, D. Gördes, A. Spannenberg and M. Beller, *J. Am. Chem. Soc.*, 2001, **123**, 8398–8399; (*b*) H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 1998, **63**, 6234–6238.

7 A. J. Kresge and P. Pruszynski, *J. Org. Chem.*, 1991, **56**, 4808–4811.

8 For the synthesis and chemical and biological importance of these heterocycles, see: (*a*) R. Dede, L. Michaelis and P. Langer, *Tetrahedron Lett.*, 2005, **46**, 8129–8131 and references cited therein; (*b*) D. Enders, H. Dyker and F. R. Leusink, *Chem.–Eur. J.*, 1998, **4**, 311–320 and references cited therein.

9 For other recent synthetic approaches to these structures, see: (*a*) P. Dambruoso, A. Massi and A. Dondoni, *Org. Lett.*, 2005, **7**, 4657–4660; (*b*) M. F. Braña, M. L. García, B. López, B. de Pascual-Teresa, A. Ramos, J. M. Pozuelo and M. T. Domínguez, *Org. Biomol. Chem.*, 2004, **2**, 1864–1871; (*c*) J. Bigorra, J. Font, C. Ochoa de Echaguen and R. M. Ortuño, *Tetrahedron*, 1993, **49**, 6717–28; (*d*) M. Kijima, K. Miyamori and T. Sato, *J. Org. Chem.*, 1988, **53**, 1719–172.

10 A referee has suggested that the homoaldolic reaction could be catalyzed by triethylamine and not by the allenolate intermediate **I**. Stirring ethyl pyruvate with a catalytic amount of triethylamine for 48 h at room temperature generates the homoaldol adduct in less than 30% yield.[11] This experimental observation confirms that alkyl propiolate is needed to generate the enolate intermediate **III** and also to drive the entire process irreversibly toward the isotetronic acid formation.

11 For a recent study of catalyzed asymmetric aldol reactions of pyruvates, see: N. Gathergood, K. Juhl, T. B. Poulse, K. Thordrup and K. A. Jørgensen, *Org. Biomol. Chem.*, 2004, **2**, 1077–1085 and references cited therein. In this study, the authors also find that amines are not suitable catalysts for the homoaldol reaction of ethylpyruvate. A copper(II) complex (metallic catalyst) is essential for the formation of the enol-form and reaction to the homoaldol product.

12 For a complete description of these alkynylide-driven domino processes see ref. 3. Note that the reaction network previous to the lactonization step comprises sequential reversible reactions; that means that early intermediates are in equilibrium with starting materials. If lactonization is fast, then the whole process is irreversible and driven to completion; in comparison, if lactonization is slow, the cycle is kinetically blocked and the enolate triggers a new domino process *via* formation of a conjugated alkynylide anion.