Synthesis of Functionalized Spiro-Heterocycles by Sequential Multicomponent Reaction/Metal Catalyzed Carbocylizations from Simple β-Ketoesters and Amides

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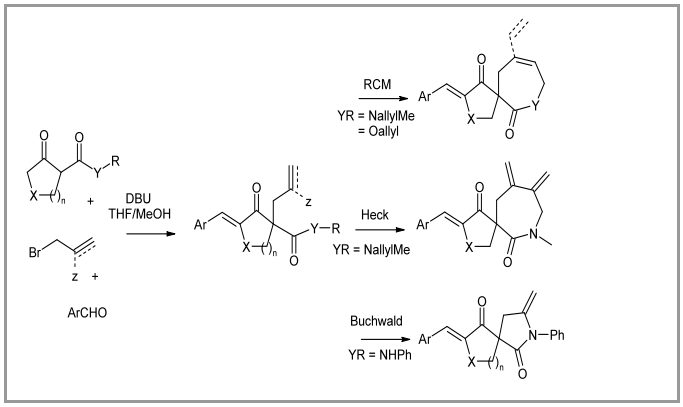
Abstract: A new strategy from simple cyclic β-ketoesters or amides involving a selective three-component reaction and a ring closing metathesis or a palladium catalyzed carbocyclization in a sequential fashion to access spiro-heterocycles is reported. This expedient two-step sequence generates compounds of significant molecular complexity and high synthetic and biological relevance from simple and readily available starting materials.

Key words: Multicomponent reactions, Ring Closing Metathesis, Heck reaction, Spiro-heterocycles, 1,3-dicarbonyl compounds.

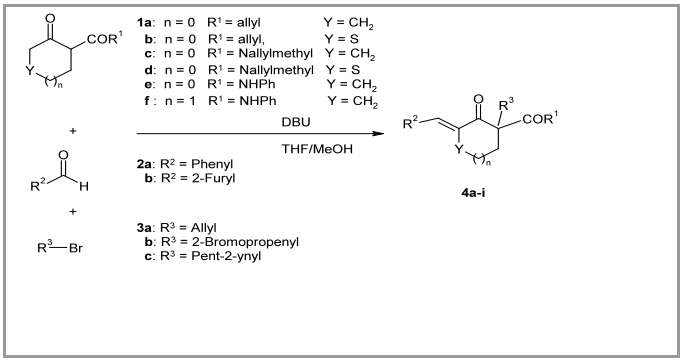
Multicomponent reactions (MCRs),[1] combining at least three different substrates in a one-pot operation, constitute nowadays a central academic and industrial investigation domain[2] in diversity-oriented synthesis[3] of functionalized heterocycles. These very efficient atom-[4] and step-economic[5] transformations also combine increase in molecular and functional complexity with practical and environmental concerns,[6] approaching quite closely the concept of an ideal synthesis.[7] In recent years, some of these transformations involving isocyanides have been combined with specific chemical postcondensation modifications that allow access to even more functionalized and specialized heterocyclic scaffolds.[8] As part of our efforts to develop new routes to construct novel heterocyclic structures with high synthetic and biological potential, we have recently reported efficient MCRs from 1,3-dicarbonyl compounds[9] including β-ketoesters and β-ketoamides.[10] In this communication we report on our efforts on extensions and postmodifications of our previously developed three-component α,γ-difunctionalization of β-ketoesters and amides[10b] using either a ring-closing metathesis (RCM) or a palladium catalyzed carbocyclization as ultimate step in the sequence for the selective elaboration of spiro-heterocycles (Scheme 1).



Scheme 1 General method for spiro-heterocycles

Although spiro-bicyclic rings are less represented in nature compared to other fused systems, they occurr widely through terrestrial plants, marine organisms or fungi and therefore have attracted considerable interest both from theoretical and synthetic points of view.[11] More particularly, the spiro-heterocyclic nucleus is present in a variety of natural products and biologically active compounds and can be of importance in the development of new medicinally relevant heterocyclic scaffolds. For example, a new class of marine toxins isolated from shelfish and dinoflagellate, such as pinnatoxins[12] and pteriatoxin[13] exhibits an azaspiro[6,5] system responsible for the biological activity. Therefore, targeting these heterocyclic cores has long been an area of intense development and still constitutes an active domain. Although numerous methods have been reported for the synthesis of functionalized spiro-heterocyclic compounds, our approach constitutes the first implication of a totally chemo-, regio-, and stereoselective MCR coupled with specific postcondensations and using simple and readily available cyclic β-ketoesters and amides.[14]

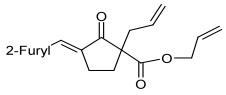
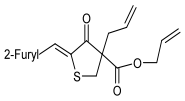
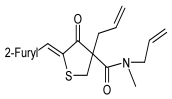
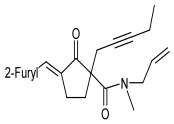
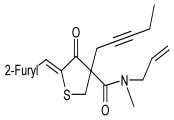
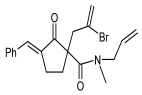
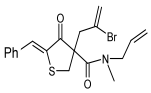
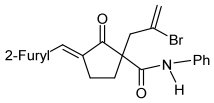
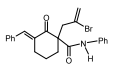
The success of our methodology rests upon the functional tolerance of the MCR both in the carbocyclic and heterocyclic series. Therefore, the new properly functionalized precursors for the carbocyclizations, bearing the required quaternary carbon atom, were readily obtained by varying the 1,3-dicarbonyl compound **1**, the aldehyde **2** and the electrophile **3** components (Scheme 2).



Scheme 2 MCRs with cyclic β-ketoesters and amides

Under general experimental conditions (Table 1) consisting in the utilization of DBU as base in MeOH, both β-ketoesters (entries 1, 2), tertiary β-ketoamides (entries 3-7), and secondary β-ketoamides (entries 8, 9) including the thioheterocyclic series gave good to excellent results.[15] The reaction proceeded smoothly either with allyl bromide **3a**, 2-bromopropenyl bromide **3b** or pent-2-ynyl bromide **3c** as electrophiles allowing the selective and modular preparation of RCM precursors **4a-e** and vinylic bromides **4f-i** required for the palladium carbocyclizations (Table 1). Compounds **4a-h** exhibit the E-configuration of the double bond as we shown in our previous paper.[10b]

Table 1 MCRs leading to spiro-heterocyclic precursors.[a]

Entry	Ketoester	Aldehyde R^2	Halide R^3	Time[h]	Product		Yield [%][b]
1	**1a**	2-Furyl	Allyl	24[c]		**4a**[10c]	72
2	**1b**	2-Furyl	Allyl	12[d]		**4b**	68
3	**1d**	2-Furyl	Allyl	48		**4c**	48
4	**1c**	2-Furyl	Pent-2-ynyl	48		**4d**	38
5	**1d**	2-Furyl	Pent-2-ynyl	48		**4e**	46
6	**1c**	Phenyl	2-Bromo-propenyl	48		**4f**	34
7	**1d**	Phenyl	2-Bromo-propenyl	48		**4g**	41
8	**1e**	2-Furyl	2-Bromo-propenyl	24		**4h**	90
9	**1f**	Phenyl	2-Bromo-propenyl	24		**4i**	39

[a] Unless otherwise specified the reactions were run in methanol at reflux. [b] Isolated. [c] The reaction was run in THF containing 10% MeOH at RT. [d] The reaction was performed at 0°C to prevent transesterification.

With this selection of new, highly functionalized precursors in hand we started to explore their chemistry taking advantage of the presence of a quaternary center for the construction of diverse spiro-structures **6** and **7** (Table 2). We looked first at the RCM starting with diallyl ketoester **4a** which we found not to be trivial. Indeed, the RCM turned to be highly catalyst dependent since only degradation was produced or no conversion was reached with up to 20 mol% of the first-generation Grubbs catalyst **5a** (Figure 1), regardless of the reaction conditions or after adding various amounts of $Ti(OiPr)_4$ in order to prevent deactivation of the catalyst.[16] Alternatively, a substantial yield of 59 % was achieved for spiro[6,4]lactone **6a** when 20 mol % of the more active second-generation Grubbs catalyst **5b** was used in refluxing CH_2Cl_2 for 30 hours (Table 2, entry 1).[17]

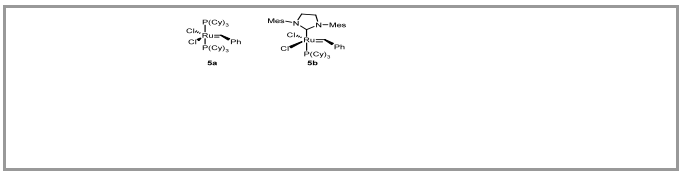
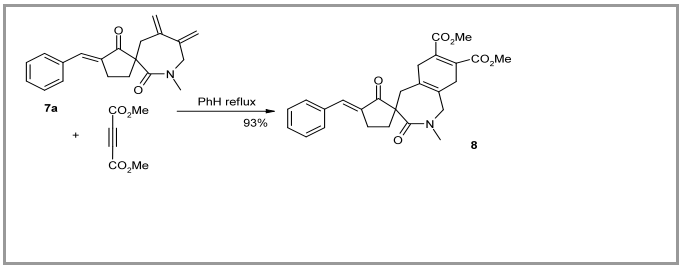


Figure 1 Grubbs Catalysts : first and second generations

On the basis of the success of this model system, the corresponding sulfur containing spirolactone **6b** and spirolactame **6c** were obtained in 56 % and 70 % yields, respectively (entries 2, 3) with surprisingly a much lower catalyst loading despite the presence of the sulfur atom. On the other hand, the enyne-RCM of precursors **4d,e** also proceeded smoothly to give the expected spiro-structures **6d,e** bearing a synthetically valuable 1,3-diene, with acceptable yields (entries 4, 5).

Alternatively, compounds **4f-i** are properly functionalized to be involved in intramolecular palladium catalyzed carbocyclizations such as Heck[18] reaction and Buchwald[19] amidation. To this end, compounds **4f,g** were easily cyclized with a comparable efficiency under standard conditions using $Pd(OAc)_2$ and PPh_3 in the presence of Et_3N in refluxing CH_3CN (entries 6, 7).[20] The expected spiro[6,4]lactams **7a,b** conserved the feature of a synthetically useful exocyclic *cis*-fixed 1,3-diene which reacted with dimethyl acetylenedicarboxylate (DMAD) in refluxing benzene to give the tricyclic skeleton **8** with 93 % yield (Scheme 3).



Scheme 3 Diels-Alder Reaction on spirolactam **7a**

Finally, bromoolefins **4h,i** were subjected to the standard catalytic amidation conditions involving the system $Pd(OAc)_2$/DPEphos to give the *exo*-methylene spiro[4,4]- and spiro[5,4]amides **7c,d** with 66% and 40% yield, respectively (entries 8, 9).

Table 2 Spiroheterocycles from compounds **4**

Entry	MCR	Conditions	Product	[%][a]
1	**4a**	20 mol%, 30 h[b]	**6a**	59
2	**4b**	10 mol%, 10 h[b]	**6b**	56
3	**4c**	5 mol%, 4 h[b]	**6c**	70
4	**4d**	10 mol%, 12 h[b]	**6d**	59
5	**4e**	5 mol%, 7 h[b]	**6e**	62
6	**4f**	PPh_3, Et_3N, 17 h[c]	**7a**	73
7	**4g**	PPh_3, Et_3N, 17 h[c]	**7b**	72
8	**4h**	K_2CO_3, 24 h[d]	**7c**	66
9	**4i**	K_2CO_3, 24 h[d]	**7d**	40

[a] Isolated. [b] All RCM were performed in anhydrous CH_2Cl_2 at reflux using catalyst **5b**. [c] Heck reactions were performed in refluxing anhydrous CH_3CN using 5 mol % of $Pd(OAc)_2$ as catalyst. [d] Buchwald amidations were performed in refluxing toluene using the system $Pd(OAc)_2$/DPEphos in the ratio 10/15 mol % as catalyst.

In conclusion, we have shown that the combination of the three-component α,,γ-difunctionalization of 1,3-dicarbonyl compounds with diene- and enyne-RCM or palladium catalyzed carbocyclizations constitutes a new, easy and modular access to a variety of functionalized spiro-heterocycles including [4,4], [5,4] and [6,4] lactone and lactam systems as potential synthetic scaffolds for the discovery of novel lead structures.

Acknowledgment

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(15) **General Procedure for MCRs**: To a solution of ketoester or ketoamide **1** (1 mmol) and DBU (3 mmol) in appropriate solvant (4 mL, table 1) was added the corresponding aldehyde **2** (1.1 mmol) and halide **3** (2 mmol). The resulting solution was stirred for the indicated time and temperature (table 1). After completion and evaporation of most of the solvent under reduced pressure, 1N solution of HCl (30 mL) was added to the oily residue. Extraction with Et_2O (3 x 40 mL) followed by successive washing with distilled water (2 x 20 mL) and brine (20 mL) gave, after drying ($MgSO_4$) and evaporation of the solvent, the crude compounds which were purified by flash chromatography on silica gel. **Physical data for compound 4b**: Yellow oil; R_f (dietyl ether 50 / petroleum ether 50) = 0.79; IR (liquid film): 2942, 1740, 1678, 1588, 1472, 1208, 1133, 927 cm^{-1}; MS : m/z (%) = $[M+H^+]$ 305 (100), 264 (13), 247 (36), 219 (12), 206 (8). ^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.5 (1H, d, *J* = 1.5 Hz), 7.35 (1H, s), 6.72 (1H, d, *J* = 3.5 Hz), 6.53 (1H, dd, *J* = 3.5, 1.5 Hz), 5.92-5.65 (2H, m), 5.32-5.13 (4H, m), 4.63 (2H, dd, *J* = 5.6, 1.0 Hz), 3.71 (1H, d, *J* = 11.2 Hz), 3.15 (1H, d, *J* = 11.2 Hz), 2.84 (1H, dd, *J* = 13.8, 7.1 Hz), 2.58 (1H, dd, *J* = 13.8, 7.6 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 197.3, 168.9, 151.6, 144.7, 131.3, 132.0, 128.2, 118.8, 115.9, 120.1, 112.9., 115.5,66.6, 60.4, 38.6, 32.7.

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(17) **General procedure for RCMs**: To a $6x10^{-3}$ M solution of spiro-heterocyclic precursors **4a-4e** in dry CH_2Cl_2, under atmosphere of argon, the Grubbs catalyst **5b** was introduced in several portions of 2% every 2 hours. The mixture was stirred at reflux and completion of reaction checked by TLC. The mixture was filtered through a pad of silica gel and celite and the crude material was purified by flash chromatography on silica gel. **Physical data for compound 6c**: Yellow solid; mp = 104-106°C; IR (liquid film): 2960, 1708, 1620, 1460, 1201, 1030 cm^{-1}; m/z (%) = $[M+H^+]$ 290 (100), 233 (17), 190 (5). ^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.53 (1H, d, *J* = 1.7 1Hz), 7.32 (1H, s), 6.67 (1H, d, *J* = 3.3 Hz), 6.49 (1H, dd, *J* = 3.3, 1.7 Hz), 5.85-5.75 (2H, m), 4.18-3.90 (2H, m) , 3.81 (1H, d, *J* = 11.7 Hz), 3.03 (3H, s), 3.00 (1H, d, *J* = 11.7 Hz), 2.98-2.89 (1H, m), 2.35-2.26 (1H, m). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 198.6, 170.2, 151.8, 144.4, 127.7, 125.8, 128.4, 112.8, 115.5, 115.0, 60.4, 49.8, 38.9, 35.1, 31.9.

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(20) **General procedure for Heck reaction**: To a $4x10^{-2}$ M solution of spiro-heterocyclic precursors **4f** and **4g** in dry acetonitrile, under atmosphere of argon, palladium acetate (4 equiv) and triphenylphosphine (8 equiv) were added, followed by triethylamine (1.2 equiv). The mixture was stirred at reflux and completion of reaction checked by TLC. The mixture was filtered through a pad of celite and the crude material was purified by flash chromatography on silica gel. **Physical data for compound 7b**: Yellow powder mp = 169-171°C; IR (liquid film): 2926, 1719, 1626, 1444, 1337, 1256, 940 cm^{-1}; m/z (%) = $[M+ H^+]$ 326, (100), 295 (3), 255 (3), 201 (3), 164 (16); ^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.64-7.34 (6H, m), 5.41 (2H, d, *J* = 16.6. 0.9 Hz), 5.02 (1H, d, *J* = 9.3 Hz), 4.72 (2H, dd, *J* =15.1. 1.1 Hz) , 4.04 (1H, dd, *J* = 11.3. 0.9 Hz), 3.57 (1H,

d, J = 15.3 Hz), 3.07 (1H, d, J = 11.2 Hz), 3.03 (3H, s), 2.98 (1H, d, J = 14.4 Hz), 2.56 (1H, d, J = 14.4 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 200.9, 169.0, 143.5, 141.8, 135.0, 130.5, 129.6, 129.5, 129.2, 128.8, 115.3, 112.8, 61.4, 54.2, 39.4, 37.1, 31.1.