ORGANIC LETTERS

2009
Vol. 11, No. 22
5314−5317

Four-Component Reactions toward Fused Heterocyclic Rings

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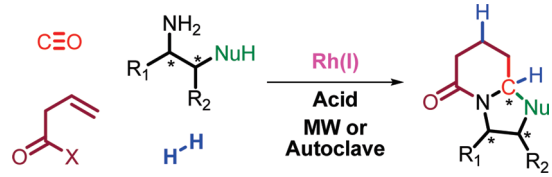
Received October 2, 2009

ABSTRACT



A multicomponent reaction between H_2, CO, an unsaturated carboxylic acid derivative, and binucleophiles has been discovered. This process represents a combination of diversity-oriented synthesis and multicomponent reactions including amidation and hydroformylation, followed by nucleophilic addition to an *N*-acyliminium ion allowing the generation of six new bonds. Using π-nucleophiles, the sequence turns into a multicomponent Pictet−Spengler reaction.

Many efforts have been devoted toward the rational design of scaffolds using guidelines for the generation of libraries in medicinal chemistry such as diversity-oriented synthesis (DOS)[1,2] or multicomponent reactions (MCRs).[3,4] Thus innovations in DOS and MCRs based on selectivity, step economy, and feasibility are actual trends in molecular science.[5]

In this respect, hydroformylation of alkenes may be a source of inspiration. However, although aldehydes produced by hydroformylation have been integrated in domino processes,[6,7] there are limited numbers of examples concerning true MCRs involving gaseous reagents.[6] As the generation of aldehydes by hydroformylation has been beneficial for several chemical processes,[8,9] we plan to experiment a MCR toward the preparation of fused lactams, popular starting materials for many chemical transformations (Figure 1).[10−13]

[†] CNRS-Université de Strasbourg.
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(1) (a) Isambert, N.; Lavilla, R. *Chem.−Eur. J.* **2008**, *14*, 8444–8454. (b) Breit, B.; Schmidt, Y. *Chem. Rev.* **2008**, *108*, 2982–2951. (c) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C. *Nat. Prod. Rep.* **2008**, *25*, 719–737. (d) Hubel, K.; Lessmann, T.; Waldmann, H. *Chem. Soc. Rev.* **2008**, *37*, 1361–1374.

(2) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56, and references therein.

(3) (a) Ugi, I.; Domling, A.; Horl, W. Multicomponent reactions in organic chemistry. *Endeavour* **1994**, *18*, 115–122. (b) Armstrong, R. M.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131.

(4) For some selected reviews, see: (a) Gonzalez-Lopez, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164–189. (b) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324–331. (c) Shestopalov, A. M.; Shestopalov, A. A.; Rodinovskaya, L. A. *Synthesis* **2008**, 1–25. (d) Banfi, L.; Guanti, G.; Riva, P.; Basso, A. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 704–714. (e) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(5) For an interesting overview on the need for innovation in multicomponent reactions, see: Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472.

(6) Mihovilovic, M. D.; Stanetty, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3612–3615.

(7) (a) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329–3365. (b) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264–275.

(8) (a) Petricci, E.; Mann, A.; Rota, A.; Schoenfelder, A.; Taddei, M. *Org. Lett.* **2006**, *8*, 3725–3727. (b) Petricci, E.; Mann, A.; Salvadori, J.; Taddei, M. *Tetrahedron Lett.* **2007**, *48*, 8501–8504. (c) Spangenberg, T; Breit, B.; Mann, A. *Org. Lett.* **2009**, *11*, 261–264.

(9) Airiau, E.; Spangenberg, T.; Girard, N.; Schoenfelder, A.; Salvadori, J.; Taddei, M.; Mann, A. *Chem.−Eur. J.* **2008**, *14*, 10938–10948.

10.1021/ol902279m CCC: $40.75
Published on Web 10/26/2009

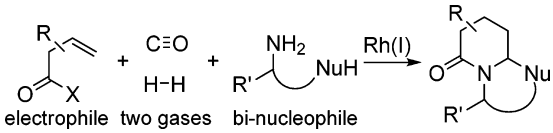
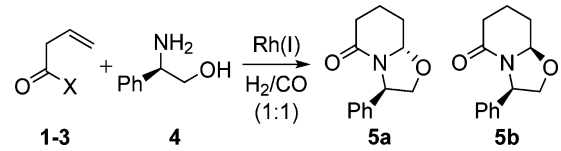


Figure 1. Domino MCR reaction orchestrated by Rh(I).

Therefore MCRs were investigated with the following four ingredients: an alkene having an acyl group, CO, H_2, and binucleophilic substrates, carrying as nucleophiles a primary amine, and either an oxygen atom or a sp^2 carbon. While the reactivity of the two gases on the alkene is orchestrated by Rh(I) to reach linear hydroformylation, the complementary reactivity of both electrophiles and nucleophiles present in the mixture should produce oxazolidinones with *the generation of six new bonds in a one-pot single step.* Bicyclic 5-6 fused lactams of this type are generally prepared using the Meyers route by thermal cyclodehydration of γ-acid-aldehydes with an amino-alcohol,[14] but the latter are tedious to prepare and sensitive to reactions conditions.[10] Herein we propose a new chemical sequence with a substantial step economy by producing in situ the two main reaction partners: the aldehydes and the secondary amides.

For the design and verification of the experimental setup of the process, various conditions were tested (Table 1). Xantphos or biphephos were selected as chelating ligands for Rh(I) to guarantee linear hydroformylation of the alkenoic acids. All reactions were conducted with an acid catalysis to promote the domino reaction.[9] To determine a suitable activation for 3-butenoic acid, *O*-Me or *O*-succinimidyl (OSu) ester was investigated. A preliminary experiment (entry 1) was performed with (*R*)-phenylglycinol **4** and OSu ester **1**, in the presence of xantphos as the hydroformylative ligand. Oxazolidinones **5a/b** were obtained from the reaction mixture,[11] the *trans* dia **5a** being the major adduct as the final cyclization is under thermodynamic control. Furthermore, with biphephos as ligand (entry 2), a better yield was obtained with a similar diastereoselectivity, and under microwave (MW) dielectric heating the results were comparable with an appreciable saving of time (1 h instead of 12 h, entry 3). From these preliminary results it can be concluded that the above designed four-ingredient reaction takes place successfully. It is worth noting that the catalytic activity of Rh(I) was maintained supress in the presence of many fuctional groups or additives. Interestingly the diastereomeric ratio of the adducts **5a/5b** depended on the acyl-activation of butenoic acid (**1**−**3**: X = OSu, OMe, OH) and on the experimental device (autoclave or MW).

Table 1. Optimization of Domino MCR with **4**



1-3 **4** **5a** **5b**

entry	X	conditions[a]	yield of **5a** (%)[b]	yield of **5b** (%)[b]
1	**1**: OSu	autoclave[c]	58	6
2	**1**: OSu	autoclave	81	8
3	**1**: OSu	MW	79	9
4	**2**: OMe	autoclave		45
5	**2**: OMe	MW	35	45
6	**3**: OH	MW	35	40

[a] Conditions for reactions carried out under MW dielectric heating: ratio **1**−**3**:**4** = 1.2:1; 7 bar H_2/CO (1:1), $Rh(CO)_2acac$ 1 mol %, biphephos 2 mol %, 150 W, max internal temperature and pressure 70 °C and 10 bar, *p*TSA 10 mol %, [amino-alcohol] = 0.04 M in THF, 1 h. Conditions for reaction carried out in a stainless steel autoclave: ratio **1**−**3**:**4** = 1.2:1, $Rh(CO)_2acac$ 1 mol %, biphephos 2 mol %, [amino-alcohol] = 0.04 M in THF, PPTS 5 mol %, 5 bar H_2/CO (1:1), 70 °C, 12 h. [b] Isolated yield. [c] Xantphos as ligand (2 mol %).

In the autoclave with the *O*-Me ester **2**, oxazolidinone **5b** (*cis* dia) was observed as the only adduct, whereas under MW irradiation a mixture of **5a** and **5b** was observed (compare entries 4 and 5). Finally with the free acid **3** (entry 6), a 1:1 mixture of **5a** and **5b** was obtained under MW dielectric heating, whereas no reaction was observed in the autoclave.

Interestingly, in both cases the dissimilar product distribution reflects two sequences of events.[12,13] With the *O*-succinimidyl **1**, amidation occurs first, followed by the hydroformylation and formation of the *N*-acyliminium derivative. Under thermodynamic control, the latter undergoes nucleophilic addition to yield the *trans* oxazolopiperidinone **5a**. With the less activated *O*-Me ester **2** and the acid **3**, the hydroformylation initiates the reaction. Then, the newly formed aldehyde reacts with the binucleophile to form mainly a *cis* disubstituted oxazolidine. Finally, amidation on the ester or acid functions delivered mainly the *cis* oxazolopiperidone **5b**. In the autoclave solely the *cis* isomer (**5b**) was obtained albeit in moderate yield.[12,13] However, under microwave irradiation, the more harsh and heterogeneous conditions gave the mixture of diasteromers (entries 5 and 6).

These preliminary experiments demonstrate that a proper choice of the acyl-activation in the MCR delivered either

(10) Meyers, A. I; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243–4246.

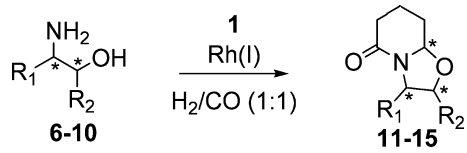
(11) For leading references on chiral non-racemic bicyclic lactams, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873. For other preparative methods, see: (c) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223–2226. (d) Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493–1496. (e) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun.* **1996**, *26*, 1605–1611. (f) Allin, S. M.; Thomas, C. I.; Allard, J. E.; Doyle, K.; Elsegood, M. R. J. *Eur. J. Org. Chem.* **2005**, *19*, 4179–4186. (g) Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661–3663. (h) Le Quement, S. T.; Nielsen, T. E.; Meldal, M. *J. Comb. Chem.* **2007**, *9*, 1060–1072.

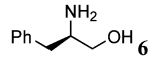
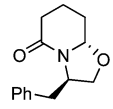
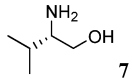
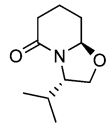
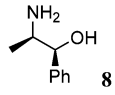
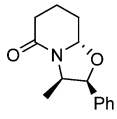
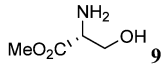
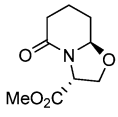
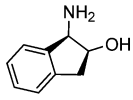
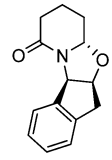
(12) Bouet, A.; Oudeyer, S.; Dupas, G.; Marsais, F.; Levacher, V. *Tetrahedron: Asymmetry* **2008**, *19*, 2396–2401.

(13) This behavior is in concordance with the results observed by Amat, who reported the formation of the *cis* isomer via a multistep sequence based on the condensation of 5-oxopentanoate with **4**. Amat, M.; Bosch, J.; Hidalgo, J.; Canto, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084.

(14) Couty, F.; Evano, G. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J., Eds.; Elsevier Ltd.: Oxford, 2008; Vol. 11, 409−499.

Table 2. Domino MCR on Various Amino-alcohols



entry	substrate	condition[a]	product	yield[b] (*trans*/*cis*)[c]
1	 **6**	**A**	 **11**	81% (83/17)
2	**6**	**B**	**11**	75% (83/17)
3	 **7**	**A**	 **12**	63% (75/25)
4	 **8**	**A**	 **13**	81% (83/17)
5	 **9**	**B**	 **14**	54% (84/16)
6	 **10**	**B**	 **15**	98% (83/17)

[a] **A**: reactions carried out in autoclave, conditions as in Table 1. **B**: reactions carried out in MW, conditions as in Table 1. [b] Isolated yields. [c] Diastereoselectivity determined by ^{1}H NMR of the crude reaction mixtures.

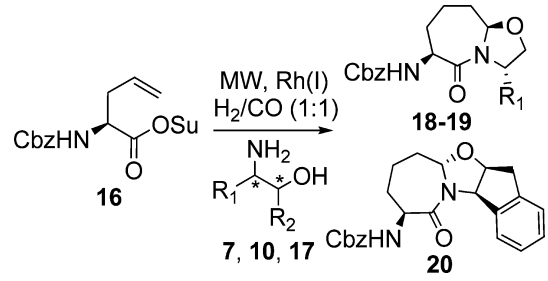
oxazolopiperidones **5a** or **5b**, in contrast to the intramolecular strategy in which **5a** was favored.[9] Finally the conditions described in entries 2 and 4 were routinely used for the hydroformylative reactions in either device, respectively.

These results prompted us to extend the procedure with olefin **1** to other amino-alcohols (**6**−**10**) (Table 2). The expected oxazolopiperidones **11**−**15** were obtained in moderate to good yields favoring always the *trans* (**11a**−**15b**) over the *cis* (**11b**−**15b**) adducts.[15] Autoclave and MW gave roughly similar results.

To expand the scope of the reaction and increase the molecular complexity, *N*-Cbz-allylglycine *O*-succinimide ester **16**, a chiral masked bielectrophile, was engaged in the MCR with chiral amino-alcohols (**7**, **10** and **17**) (Table 3). As expected 7,5-fused bicyclic or tetracyclic heterocycles **18**, **19**, or **20** were obtained in good yields and diastereomeric ratios. The *trans* isomer was always the major adduct.

(15) The diastereomers were separable by chromatography, allowing isolation of the major adduct with the yields reported in Table 2. It was possible to isolate also the *cis* isomer of compounds **11**−**15**.

Table 3. Domino MCR with *N*-Cbz-Allylglycine *O*-Su Ester **16**



entry	substrate[a]	product	yield (%)[b] (*trans*/*cis*)[c]
1	(*S*)-phenylglycinol **17**	**18**: R_1 = Ph	76 (86/14)
2	**7**	**19**: R_1 = *i*Pr	84 (83/17)
3	**10**	**20**	80 (88/12)

[a] Reactions carried out in MW, conditions as in Table 1. [b] Isolated yield. [c] Diastereoselectivity determined by ^{1}H NMR of the crude reaction mixtures.

It has been shown that α-amino acids are possible ligands for Rh(I) during the hydroformylation of alkenes;[16] nevertheless we decided to test amino acids **21**−**25** as possible binucleophilic partners in the MCR, in noticing that, as zwitterions, their reactivity as nucleophiles can be questioned. In return the preparation of oxazolo-pyridinediones can be at hand in a one-step procedure (Table 4). A literature survey revealed that this class of compounds is scarcely reported albeit their potentials for further transformations.[12,17] Thus using the optimal conditions described before, the reaction of the OSu ester **1** and D-phenylalanine (**21**) gave compound **26** as a single diastereomer in a good yield (69%).[18] Applied to several aminoacids such as (*R*)-phenylglycine (**22**), L-valine (**23**), and L-methionine (**24**), only the corresponding *trans* oxazolopyridine-diones **26**−**29** were obtained as single diastereomers, as extrapolated from a single crystal X-ray[19] obtained for **27**. Both autoclave and microwave dielectric heating produced similar results. This one-pot procedure is particularly attractive for the obtention of original scaffold by reacting allylglycine derivative **16** with L-phenylalanine (**25**), **30** is obtained as a single diasteromer in 65% yield.

Clearly bicycle **30** is amenable to an azepinone with three different points of molecular diversity.[12,17a,20] The stereochemistry of the adducts **26**−**30** arising from the above MCR with the α-amino acids indicates a thermodynamic control.

(16) Paganelli, S.; Marchetti, M.; Bianchin, M.; Bertucci, C. *J. Mol. Catal. A: Chem.* **2007**, *269*, 234–239.

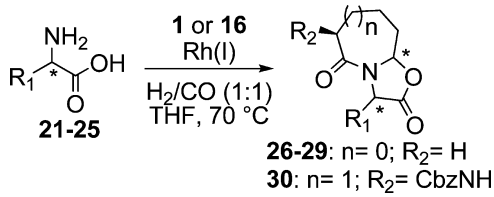
(17) (a) Bassas, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817–2820. (b) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; DiMarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348–2355.

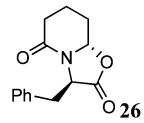
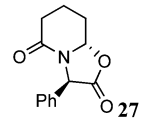
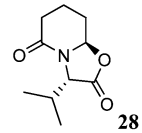
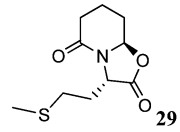
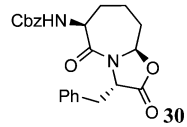
(18) This high selectivity can be explained with the higher lability of the bond on C8a due to the presence of the carbonyl. This situation allows a rapid equilibration toward the *trans* isomer even in the presence of small amounts of acid .

(19) See Supporting Information for ORTEP of **27**.

(20) 3-Aminoazepanones substituted in position 7 have been previously described in several patents as structures of pharmaceutic interest. See for example: Burgey, C. S.; Deng, Z. J.; Nguyen, D. N.; Paone, D. L. V.; Shaw, A. W.; Williams, T. M. WO 2004092166 A2 20041028. Knaup, G. DE 10020818 A1 20011031

Table 4. Domino MCR of **1** with Various Amino Acids



entry	amino-acid	conditions[a]	product	yield[c]
1	**21**: D-phenylalanine	Autoclave, **1**, PPTS 5 mol %	 **26**	69%
2	**22**: (*R*)-phenylglycine	Autoclave, **1**, PPTS 10 mol %	 **27**	54%[b]
3	**23**: L-valine	autoclave, **1**, *p*TSA 10 mol %	 **28**	70%
4	**24**: L-methionine	autoclave, **1**, PPTS 5 mol %	 **29**	71%
5	**24**: L-methionine	MW, **1**, *p*TSA 10 mol %	**29**	70%
6	**25**: L-phenylalanine	MW, **16**, *p*TSA 10 mol %	 **30**	65%

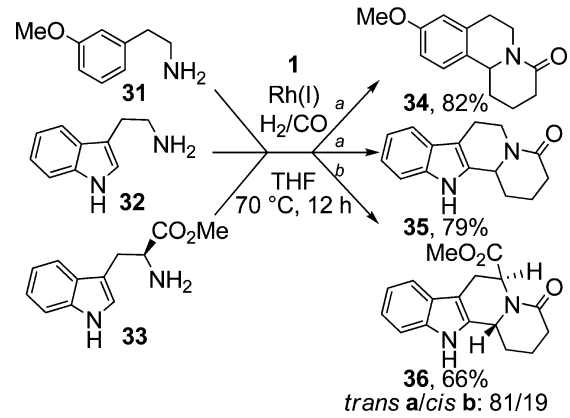
[a] Conditions as in Table 1. [b] Reaction carried out in toluene. [c] Diastereoselectivity *trans*/*cis* > 95/5 in all cases, determined by ^{1}H NMR of the crude reaction mixture.

More work is necessary to clarify the chronology of the events.

Finally as transient *N*-acyliminium ions are powerful electrophiles, the possibility to extend the MCRs to a one-pot Pictet−Spengler reaction was examined (Scheme 1).[21] For that purpose, enriched aromatic rings such as 3-MeO-phenethylamine (**31**), tryptamine (**32**), or *O*-Me-tryptophane (**33**) were selected as *C*-nucleophile partners. Running the MCR with arylamines **31** and **32** in presence of BF_3•Et_2O, compounds **34** and **35** were isolated as the expected Pictet−Spengler adducts in good yields.

(21) For a recent application, see: Chiou, W.-H.; Lin, G.-H.; Hsu, C.-C.; Chaterpaul, S. J.; Ojima, I. *Org. Lett.* **2009**, *11*, 2659–2662.

Scheme 1. One-Pot, MCR/Pictet−Spengler Reaction



[a] $Rh(CO)_2acac$ 1 mol %, biphephos 2 mol %, 5 bar H_2/CO (1:1), BF_3•Et_2O 20 mol % [b] $Rh(CO)_2acac$ 1 mol %, biphephos 2 mol %, 5 bar H_2/CO (1:1), *p*TSA 10 mol %.

For **33**, the reaction was performed in presence of *p*TSA and a mixture of the tetracyclic adducts **36a,b** was obtained with a good yield, **36a** (*trans* dia) being the major adduct.[9] As expected, the MCR/Pictet−Spengler reaction allowed a very straightforward access to *N*-containing polycyclic compounds starting from carefully designed starting materials.

In conclusion a new MCR has been discovered employing a latent bielectrophile (unsaturated acid derivative) and binucleophiles. In an autoclave or under MW irradations, a sequence of four reactions occurred in situ, namely, amide bond formation, linear hydroformylation, intermolecular collapse to an *N*-acyliminium and a final nucleophilic attack. In this process *six new bonds were created in a single step* delivering fused heterocycles with good control of the diatereoselectivity. This process represents a combination of DOS and MCR involving gaseous reagents (CO and H_2) that are scarcely exemplified but have great potentialities.

Acknowledgment. This work was supported by the Ministère délégué à l'Enseignement Supérieur et à la Recherche (E.A.) and by MIUR (Rome) within the PRIN projects 2008.

Supporting Information Available: Detailed experimental procedures and spectral and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902279M