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A New Multicomponent Domino Reaction of 1,3-Dicarbonyl Compounds: One-Pot Access to Polycyclic *N*/*O*-, *N*/*S*-, and *N*/*N*-Aminals

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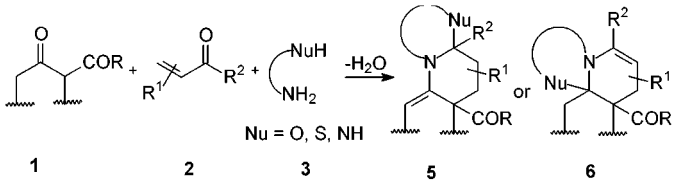
ABSTRACT



The first multicomponent domino transformation between 1,3-dicarbonyls 1, α,β-unsaturated compounds 2, and functionalized amines 3 is described, providing a one-pot access to fused polyheterocyclic or spiropolyheterocyclic compounds 5 or 6 bearing an aminal function by formation of up to three new cycles, five novel bonds, and up to six stereogenic centers.

Since the first multicomponent reaction (M-CR) reported in 1850 by Strecker,[1] this methodology emerged as a powerful strategy in modern synthetic organic chemistry.[2] Besides their efficiency in terms of atom economy, time savings, and environmental friendliness, such one-pot transformations lead to the facile creation of several new covalent bonds and have been extensively used in liquid-phase as well as in solid-phase chemistry for the rapid assembly of complex heterocyclic structures of importance for pharmaceutical development.[3] For these reasons, the discovery of new reaction sequences able to produce valuable elaborated compounds constitutes a challenge both from academic and industrial points of view.[4]

In this context, utilization of 1,3-dicarbonyls has not been the center of much interest[5] and apart from the well-known Hantzsch,[6] Biginelli,[7] and Robinson−Schöpf[8] reactions and

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(1) Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27.

(2) For reviews on M-CRs, see: Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. Tietze, L. F.; lieb, M. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363. Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255. Tietze, L. F; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

(3) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449.

(4) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.

(5) For a comprehensive review on synthetic utilizations of β-ketoesters, see: Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 5.

(6) Hantzsch, A. *Liebigs Ann. Chem.* **1882**, *215*, 1; *Ber. Deutsch. Chem. Ges.* **1890**, *23*, 1474. For a recent example of pyrroles synthesis using M-CRs, see: Ranu, B. C.; Hajra, A.; Jana, U. *Synlett* **2000**, 75.

(7) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962. For a recent account, see: Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.

(8) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762. Schöpf, C. *Angew. Chem.* **1937**, *50*, 779 and 797. For a more recent utilization, see: List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

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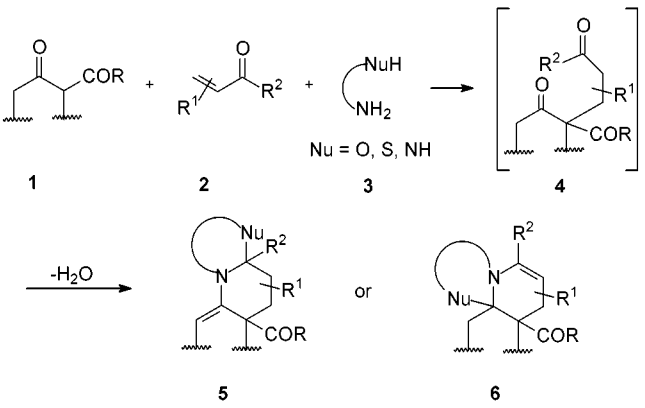
more recently Tietze synthesis of dihydropyrans[9] no other application has been reported to date. Accordingly, we now propose a new and general one-pot three-component domino transformation, for the preparation of functionalized polycyclic aminals. Interestingly, acetals and mixed acetals, which are of great synthetic value, have been extensively studied over the years[10] and still constitute important synthetic intermediates.[11] Moreover, fused polycyclic structures including *N*/*O*- and *N*/*N*-aminals are found in biologically active natural and unnatural compounds such as alkaloids[12] and polyhydropyrroloimidazoles or polyhydroimidazopyridines,[13] which also constitute effective intermediates for the preparation of chiral pyrrolidines and piperidines.[14]

Our continuing efforts directed to the development of new domino transformations initiated by Michael addition[15] prompted us to study the reactivity of 1,3-dicarbonyls **1** toward α,β-unsaturated carbonyl compounds **2** in the presence of ω-functionalized primary amines **3**. The idea was to use amines **3** both as basic promoters for the Michael addition and also as a selective acetalizing agent for the 1,5-dicarbonyl intermediate **4**, leading to either fused cyclic aminals **5** or spirocyclic structures **6** depending on the structure of the nucleophilic amine (Scheme 1).[16]

To test this hypothesis, we first tried to promote the transformation by simply heating a mixture of carbethoxypiperidone **1a**, acrolein (**2a**), and 1,2-diaminoethane (**3a**) in toluene unfortunately without success even after 24 h at reflux (Table 1, run 1). Similarly, use of trimethyl orthoformate (TMOF) as dehydrating agent, either at room temperature or at reflux for prolonged time, also proved unsuccessful (run 2). Gratifyingly, addition of 4 Å molecular sieves

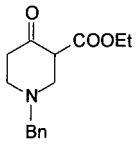
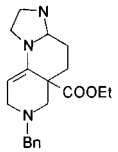
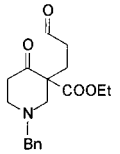
Scheme 1



(MS) afforded the expected fused tricyclic aminal **5a** in 60% isolated yield as a single diastereomer (run 3). On the other hand, although no reaction was observed between **1a** and acrolein (**2a**) in the absence of any other additive (run 4), addition of 4 Å MS resulted in the formation of the corresponding Michael adduct **4a** in 20% yield (run 5). These results clearly show the crucial action of molecular sieves, which act as the initiator for the Michael addition.

Under these neutral experimental conditions, the overall transformation proved to be general, and a simple filtration

Table 1. Effect of Experimental Conditions on M-CR with **1a** and Acrolein (**2a**)

run	conditions[a]	product	yield (%)[b]
1	**3a**	 **1a**	-
2	**3a**, TMOF[c]	**1a**	-
3	**3a**, 4Å MS	 **5a**	60
4	-[d]	**1a**	-
5	4Å MS	 **4a**	20[e]

[a] Unless otherwise noted, all reactions were performed in refluxing toluene for 24 h. [b] Isolated. [c] Performed both at room temperature and reflux. [d] No additive. [e] Unreacted **1a** was also recovered.

(9) Tietze, L. F.; Hippe, T.; Steinmetz, A. *Synlett* **1996**, 1043. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. Tietze, L. F.; Evers, H.; Töpken, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 903.

(10) For *N*/*O*-aminals, see: Büchel, K. H.; Falbe, J.; Hagemann, H.; Hanack, M.; Klamann, D.; Kreher, R.; Kropf, H.; Regitz, M.; Schaumann, E. In *Houben-Weyl Methoden der organische Chemie*; Hagemann, H., Klamann, D., Eds.; Georg Thieme Verlag; Stuttgart, 1991; E14a/2. For *N*/*S*- and *N*/*N*-aminals, see: Pawlenko, S.; Lang-Fugmann, S. In *Houben-Weyl Methoden der organische Chemie*; Hagemann, H., Klamann, D., Eds.; Georg Thieme Verlag: Stuttgart, 1992; E14a/3.

(11) *N*/*N*-Aminals: (a) Alexakis, A.; Mangeney, P.; Lensen, N.; Tranchier, J. P.; Gosmini, R.; Raussou, S. *Pure Appl. Chem.* **1996**, *68*, 531. (b) Jung, M. E., Huang, A. *Org. Lett.* **2000**, *2*, 2659. *N*/*O*-Aminals: (c) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (d) François, D.; Poupon, E.; Lallemand, M.-C.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 3209. (e) Mulzer, J.; Langer, O.; Hiersemann, M.; Bats, J. W.; Buschmann, J.; Luger, P. *J. Org. Chem.* **2000**, *65*, 6540. *N*/*S*-Aminals: (f) Holmes, C. P.; chinn, J. P.; Look, G. C.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328.

(12) elAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757. Zhu, X.; Greig, N. H.; Holloway, H. W.; Whittaker, N. F.; Brossi, A.; Yu, Q.-S. *Tetrahedron Lett.* **2000**, *41*, 4861.

(13) Katritzky, A. R.; Qiu, G., He, H.-Y.; Yang, B. *J. Org. Chem.* **2000**, *65*, 3683 and references therein.

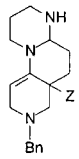
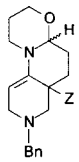
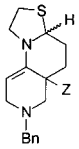
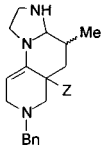
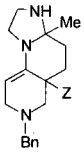
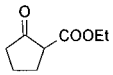
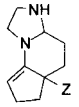
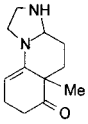
(14) For a recent example, see: Andrés, J. M.; Herráiz-Sierra, I.; Pedrossa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem.* **2000**, 1719.

(15) For a recent account, see: Rodriguez J. *Synlett* **1999**, 505. Durand, A. C.; Dumez, E.; Rodriguez, J.; Dulcère, J. P. *Chem. Commun.* **1999**, 2427. Durand, A. C.; Rodriguez, J.; Dulcère, J. P. *Synlett* **2000**, 731.

(16) For examples of the formation of fused bicyclic acetals and aminals starting from α,ω-dicarbonyl derivatives and their synthetic applications, see inter alia: Okawara, T.; Ehara, S.; Matsumoto, S.; Okamoto, Y.; Furukawa, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2160. Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth.* **1992**, *70*, 54. Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. See also refs 11d and 12.

through a short pad of Celite furnished good yields of fused polycyclic aminals **5** with generally very high chemical purity (Table 2). A similar result is obtained with 1,3-propylamine

Table 2. M-CR Leading to Polycyclic *N*/*N*-, *N*/*O*-, and *N*/*S*-Aminals **5** (Z = COOMe)[a]

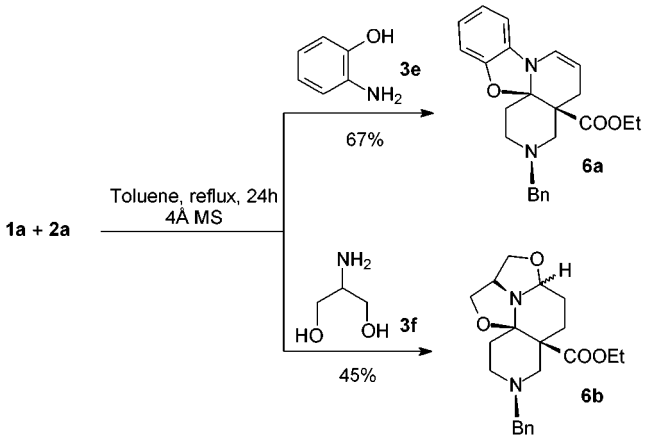
run	1	2	3	product 5	yield (%)[b]
					
		R^1; R^2	n; X		
1	**1a**	**2a**:H; H	**3b**: 1; NH_2	**5b**		65
2	**1a**	**2a**	**3c**: 1; OH	**5c**		80[c]
3	**1a**	**2a**	**3d**: 0; SH	**5d**		66[c]
4	**1a**	**2b**: Me; H	**3a**: 0; NH_2	**5e**		82[c]
5	**1a**	**2c**: H; Me	**3a**	**5f**		85
6	**1b**		**2a**	**3a**	**5g**		36
7	**1c**		**2a**	**3a**	**5h**		52

[a] Reactions were performed on a 1 mmol scale using 25 mL of THF, 6 g of 4 Å MS, and a **1**/**2**/**3** ratio of 1/1.5/1. [b] Isolated. [c] Two isomers respectively in 1.2/1, 2/1, and 1.2/1 ratio.

(**3b**) (run 1), and as expected 1,3-hydroxyamine **3c** or thiolamine **3d** gives the corresponding mixed acetals **5c** and **5d** in satisfactory yields (runs 2, 3). Other electrophiles such as methacrolein (run 4) and methyl vinyl ketone (run 5) also give the expected M-CR, and carbocyclic five-membered ring ketoester **1b** (run 6) or cyclic 1,3-dione **1c** (run 7) leads to the formation of the corresponding aminals **5g**,**h** in moderate yields.

Interestingly enough, when *o*-aminophenol (**3e**) is used, the reaction of **1a** with acrolein also proceeds cleanly to give spiroaminal **6a**, exclusively, in 67% yield as a single diastereomer (Scheme 2).[17] This result can be explained by

Scheme 2



invoking a stereoelectronic control due to the presence of the aromatic ring, which prevents the formation of the corresponding fused tetracyclic isomer.[18] Finally, both reactive sites can be functionalized simultaneously by using 2-amino-1,3-propanediol (**3f**) as a partner in our new M-CR. This leads to the formation of three new cycles and five new bonds in a one-pot process, giving the tetracyclic structure **6b** bearing six stereogenic centers as a 2.5/1 mixture of only two diastereomers (Scheme 2).[19]

Mechanistically speaking, we assume that the overall process, during which up to three new cycles and five new bonds are created, is initiated by a direct Michael addition of the 1,3-dicarbonyl compound to the α,β-unsaturated carbonyl derivative promoted by the presence of MS to give adduct **4**. Then, the chemoselective formation of both an aminal and an iminium intermediate obtained via the corresponding aldimine can be invoked to explain the formation of the tri- and tetracyclic aminals **5** and **6** (Scheme 3). Also in agreement is the fact that when 1,5-dicarbonyl intermediate **4a**[20] is reacted with **3b**, the expected aminal

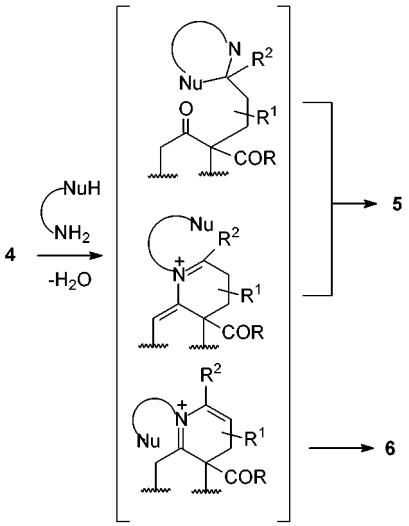
(17) The stereochemistry shown rests upon extensive NMR study including NOESY interactions, see Supporting Information.

(18) Molecular models show that due to the rigid structure of the aromatic ring the approach leading to the fused aminal does not present an optimal C−O orbitals overlap.

(19) The proposed stereochemistry for **6b** is not yet elucidated but can be deducted by analogy with **6a**.

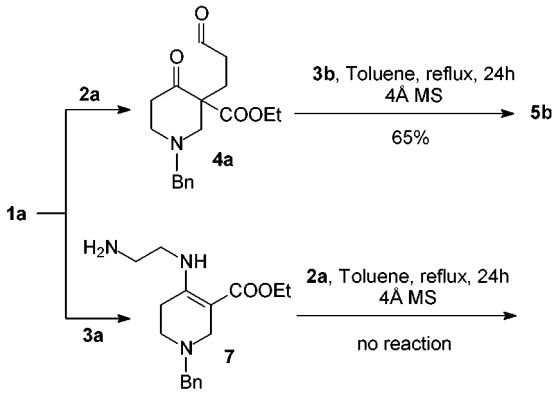
(20) Easily obtained by reaction of **1a** with acrolein in the presence of Dowex resins: Simon, C. Ph.D. Thesis, in progress.

Scheme 3



5b is isolated in 65% yield as only one diastereomer (Scheme 4). On the other hand, while Michael addition of enaminoesters proceeds under specific conditions,[21] another mechanistic pathway involving such intermediates can be ruled out since we have shown that the cyclic enaminoester **7** easily obtained from **1a** and **3a** was unreactive toward acrolein (**2a**) under our standard experimental conditions (Scheme 4). Finally, although it is known that acyclic 1,3-dicarbonyls react with 3-substituted 1-aza-1,3-butadienes under acidic conditions,[22] it has also been reported that simple enimines derived from acrolein or α,β-unsaturated ketones were not isolable[23] and therefore are likely not to be reactive intermediates in our M-CR.

Scheme 4



The extremely simple, economical, and environmentally safe experimental conditions which do not require any harmful reagent and only produce water as a byproduct make this new multicomponent domino reaction of 1,3-dicarbonyls a synthetically attractive and versatile approach for the rapid construction of functionalized polycyclic heteroatomic compounds of potential biological interest.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and mass spectral analyses for compounds **4**−**7** including a NOESY experiment for compound **6a**. This material is available free of charge via Internet at http://pubs.acs.org.

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(21) d'Angelo, J.; Cavé, C.; Desmaële, D.; Dumas, F. *Trends Org. Chem.* **1993**, *4*, 555. Guingant, A. *Advances in Asymmetric Synthesis*; JAI Press Inc.: Greenwich, CT, 1997; Vol. 2, p 159. Revial, G.; Lim, S.; Viossat, B.; Lemoine, P.; Tomas, A.; Duprat, A. F.; Pfau, M. *J. Org. Chem.* **2000**, *65*, 4593.

(22) Geirsson, J. K. F.; Gudmundsdottir, A. D. *Acta Chem. Scand.* **1989**, *43*, 618.

(23) Geirsson, J. K. F.; Johannesdottir, J. F.; Jonsdottir, S. *Synlett* **1993**, 133. Geirsson, J. K. F.; Johannesdottir, J. F. *J. Org. Chem.* **1996**, *61*, 7320.