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Enol Esters: Versatile Substrates for Mannich-Type Multicomponent Reactions

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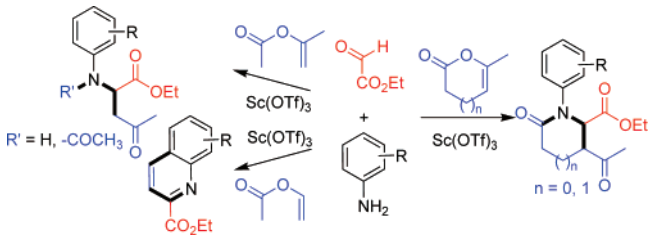
ABSTRACT



The interaction of cyclic enol esters with diversely substituted anilines and ethyl glyoxalate yields, under $Sc(OTf)_3$ catalysis, disubstituted *N*-aryl lactams in a multicomponent reaction. The protocol allows access to the trans stereoisomers after an epimerization of the initial mixture in which the cis isomers predominate. Vinyl acetate yields quinoline derivatives, whereas isopropenyl acetate leads to the corresponding Mannich adducts.

Multicomponent reactions (MCRs) constitute a powerful tool in modern organic chemistry, providing access to a variety of complex structures in a straightforward manner.[1] Among MCRs, the Povarov reaction (reaction of an aniline, an aldehyde, and an activated olefin to yield tetrahydroquinolines) is especially relevant since its robustness allows for multiple variations of each component, affording a broad array of scaffolds.[2] The use of diverse sources of enamines and enol ethers in this transformation has recently been disclosed.[3,4] With the aim of expanding the synthetic versatility of the Povarov reaction, we sought to use enol esters as the electron-rich alkene. Taking into account the participation of different enol-type species in the mechanistically related Mannich processes,[5,6] we naively assumed that the product of this reaction would be the corresponding Povarov adduct

(1) (a) For an overview, see: *Multicomponent reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. For recent reviews, see: (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (e) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (g) Also see: Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266.

(2) (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656. (b) For a recent result, see: Legros, J.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D. *Synlett* **2006**, 1899.

(3) (a) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; Walker, A. D. *Tetrahedron* **2006**, *62*, 3977. (b) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913. (c) Carranco, I.; Díaz, J. L.; Jiménez, O.; Vendrell, M.; Albericio, F.; Royo, M.; Lavilla, R. *J. Comb. Chem.* **2005**, *7*, 33. (d) Lavilla, R.; Bernabeu, M. C.; Carranco, I.; Diaz, J. L. *Org. Lett.* **2003**, *5*, 717.

(4) For instance, see: (a) Baudelle, R.; Melnyck, P.; Déprez, B.; Tartar, A. *Tetrahedron Lett.* **1998**, *54*, 4125. (b) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Biotechnol. Bioeng.* **1998**, *61*, 23. (c) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462. (d) Kumar, R. S.; Nagarajan, R.; Perumal, P. T. *Synthesis* **2004**, 949. (e) Jiménez, O.; de la Rosa, G.; Lavilla, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6521.

(5) For recent reviews of the Mannich reaction, see: (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045. (c) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Yamamoto, H., Pfaltz, A., Eds.; Springer: Berlin, 2004; Supplement 1, Chapter 29.5.

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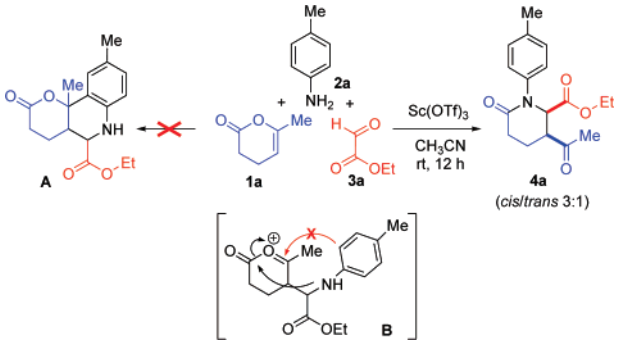
Scheme 1. Proposed Mechanism of the New MCR



(**A**, Scheme 1) containing the expected lactone moiety. However, when we treated 3,4-dihydro-6-methyl-2*H*-pyran-2-one (**1a**) with *p*-toluidine (**2a**) and ethyl glyoxalate[7] (**3a**) under $Sc(OTf)_3$ catalysis[8] in CH_3CN at room temperature, we were delighted to find that the major product was the *N*-aryl lactam **4a** (25%),[9] isolated as a mixture of cis and trans isomers (Scheme 1).[10]

This three-component synthesis of *N*-aryl lactams[11] may be rationalized considering the sequential mechanism accepted for the Povarov reaction, in which the first Mannich-type step yields intermediate **B** (Scheme 1). Instead of suffering the Friedel−Crafts termination as in the Povarov process, **B** undergoes a presumably faster lactamization, whereby reaction of the nucleophilic nitrogen at the activated carbonyl group closes the heterocyclic ring and releases the acetyl moiety. The reaction yielded **4a** as a 3:1 mixture of diastereoisomers, which was difficult to separate by standard flash chromatography. However, using preparative HPLC, both species could be purified and their relative stereochemistry determined. NMR studies did not enable structural elucidation due to nondiagnostic coupling constants and NOEs. Crystals of the major isomer were ultimately obtained from the corresponding reaction with *p*-methoxyaniline and then submitted to X-ray diffraction which revealed the cis stereochemistry for this compound (**4c**, Figure 1). No efforts to improve the *natural* diastereoselectivity of this process were made.[12]

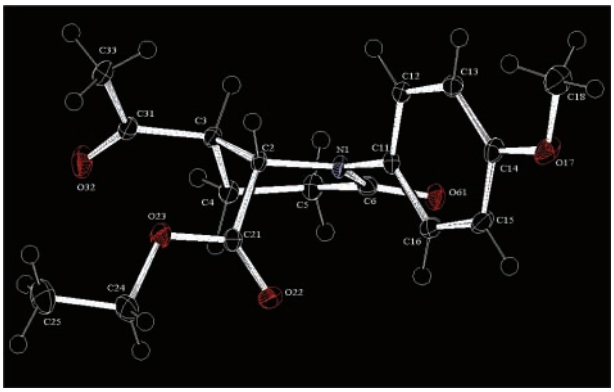
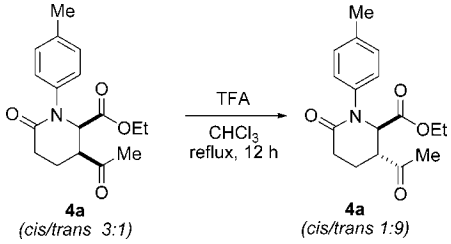


Figure 1. ORTEP diagram of the kinetic product *cis*-**4c**.

Moreover, the observation that under mild acidic conditions ($CDCl_3$) the cis diastereoisomer slowly, but progressively, equilibrates with the trans stereoisomer prompted us to test a thermodynamic acidic epimerization as a method to improve the stereoselectivity of the MCR in a practical manner. We thus monitored a solution of the kinetic mixture of **4a** (cis/trans 3:1) with TFA (20%) and observed that, after 24 h at reflux, the cis/trans ratio switched to 1:9, as determined by ^1H NMR (Scheme 2).

Scheme 2. Thermodynamic Epimerization of **4a**



In some experiments, the corresponding acyclic amino acid was formed in significant amounts due to hydrolysis of the putative Mannich intermediate **B** (see Scheme 1). We attempted to minimize this side reaction by using different solvents (THF, DCM, etc.), catalysts [$InCl_3$, $Yb(OTf)_3$, $Ce(OTf)_3$, etc.] and dehydrating agents (molecular sieves, anhydrous Na_2SO_4 or $MgSO_4$) but obtained only moderate improvements. To increase the yields, we tested in situ activation of the carboxylic acid moiety with $SOCl_2$ followed by treatment with pyridine to promote the lactamization. This led to the improved formation of **4a** (40%) in a one-pot protocol. On the other hand, the same MCR performed with 3-fold excess of the affordable enol ester component gave 45% yield. Finally, the combined use of $Yb(OTf)_3$, TMSCl,[13]

(6) (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195. (b) Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A. *Org. Biomol. Chem.* **2004**, *2*, 2451.

(7) (a) Meester, W. J. N.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2003**, 2519. (b) Taggi, A. E.; Hafez, A. M.; Leckta, T. *Acc. Chem. Res.* **2003**, *36*, 10.

(8) (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (b) Longbottom, D. *Synlett* **1999**, 2023. (c) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.

(9) Minute amounts of compound **A** were detected in some experiments (NMR and MS evidence).

(10) To the best of our knowledge, this is an unreported transformation. For a related process, see: Baydar, A. E.; Boyd, G. V.; Monteil, R. L.; Lindley, P. F.; Mahmoud, M. M. *Chem. Commun.* **1976**, 650.

(11) For the stepwise synthesis of these compounds, see: (a) Takei, H.; Fukuda, Y.; Sugaya, K.; Taguchi, T.; Kawara, T. *Chem. Lett.* **1980**, 1307. (b) Kobayashi, S.; Akiyama, R.; Moriwaki, M. *Tetrahedron Lett.* **1997**, *38*, 4819. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (d) For the *N*-arylation of amides, see: Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (e) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743. (f) Burdzhiev, N. T.; Stanoeva, E. R. *Tetrahedron* **2006**, *62*, 8318.

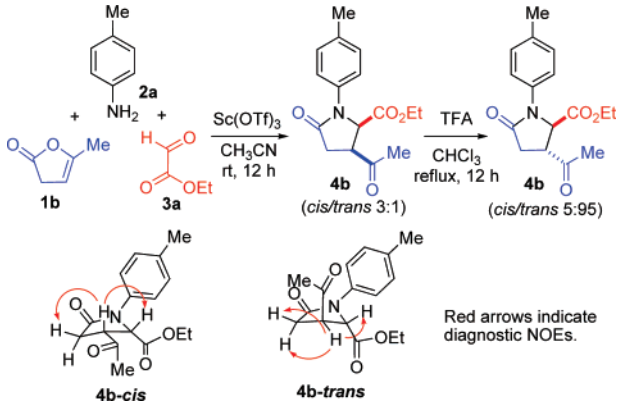
(12) This ratio of stereoisomers seems to be the usual outcome for this kind of processes. For related results, see refs 3 and 4.

(13) For a recent example, see: More, S. V.; Sastry, M. N. V.; Yao, C.-F. *Synlett* **2006**, 1399.

molecular sieves 4 Å, and anhydrous Na_2SO_4 afforded, after the in situ $SOCl_2$ cyclization, a respectable 65% yield of lactam **4a**.

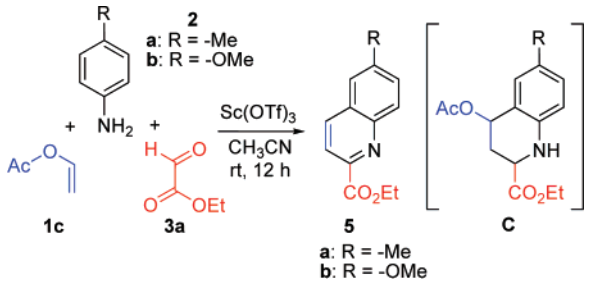
Similarly, the interaction of α-angelicalactone (**1b**), **2a**, and **3a** afforded the expected *N*-aryl 5-membered lactam **4b** (cis/trans 3:1, 31% yield, Scheme 3), which was purified by preparative HPLC.

Scheme 3. Synthesis and Epimerization of *N*-Aryl Lactam **4b**



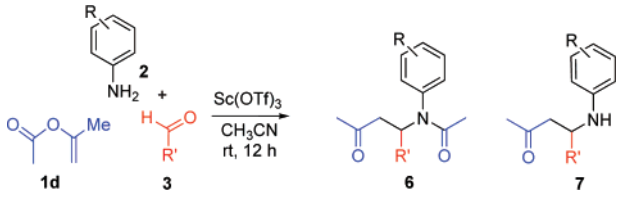
The relative stereochemistry of these compounds was established on the basis of monodimensional NOEs of pure diastereoisomers. The epimerization in acidic conditions was also observed in these series and again favored the trans isomer.[14]

Scheme 4. Quinoline Formation from Vinyl Acetate (**1c**)



We further explored the enol ester range for this MCR. Vinyl acetate (**1c**) under the same conditions afforded the quinolines **5a**[15] (R = Me, 10% unoptimized, Scheme 4) and **5b**[16] (R = OMe, 31% unoptimized). Loss of the methyl substituent at the olefin moiety dramatically affects the course of the reaction. The cyclization of the intermediate cationic species (type **B**, Scheme 1) on the activated aromatic ring would give a Povarov adduct (**C**) which ends up, presumably after spontaneous AcOH elimination and oxidation, in the fully aromatic nucleus **5**. Although the quinoline formation is precedented from a MCR involving enol ethers, aldehydes, and anilines, this transformation requires an additional acidic treatment of the initial adduct.[17]

Table 1. MCRs with Isopropenyl Acetate **1d**



entry	R	R′	compd	yield (%)
1	4-Me	CO_2Et	**6a**	20
2	4-CO_2Et	CO_2Et	**6b/7b**	9, 33
3	4-NO_2	CO_2Et	**7c**	74
4	4-NO_2	4-NO_2-Ph	**7d**	35
5	4-NO_2	4-Cl-Ph	**7e**	63
6	2,4-diNO_2	4-Cl-Ph	**7f**	76

In sharp contrast with analogous processes using enol ethers, in this MCR the aldehyde range seems to be restricted to ethyl glyoxalate: even activated (electron-deficient) aromatic aldehydes afforded very low yields of the expected lactams upon interaction with enol esters **1a** and **1b**. On the other hand, useful MCRs were observed with isopropenyl acetate (**1d,** Table 1), although loss of the acetyl moiety was the major pathway in many cases. *N*-Arylated amides **6** and amino ketones **7** were thus prepared from the corresponding interaction of **1d**, anilines, and either ethyl glyoxalate or aromatic aldehydes. Interestingly, no reports of Mannich reactions using enol esters were recorded in the literature.[18]

Finally, we explored the range of the amine component. Primary aliphatic amines were unreactive under the standard conditions. However, a wide range of diversely functionalized (activated and deactivated) anilines afforded the desired *N*-aryl γ- and δ-lactams (Table 2).

In particular, we have determined the reactivity of toluidine (entries 1 and 2), anisidine (entries 3 and 4), *p*-bromo- and *p*-chloroanilines (entries 5−7), and ethyl *p*-aminobenzoate (entry 8). Even strongly deactivated aromatic rings (*m*- and *o*-nitroanilines, entries 9 and 10) afforded the expected adducts, although in low yield in the latter case. We also observed double-lactamization processes using *p*-diaminobenzene.[19]

In conclusion, we have described the scope and limitations of the use of enol esters in Mannich-type MCRs. Although

(14) In agreement with preliminar calculations (AM1) on the relative stability of cis and trans isomers.

(15) The corresponding carboxylic acid is described: Buehler, C. A.; Edwards, S. P. *J. Am. Chem. Soc.* **1952**, *74*, 977.

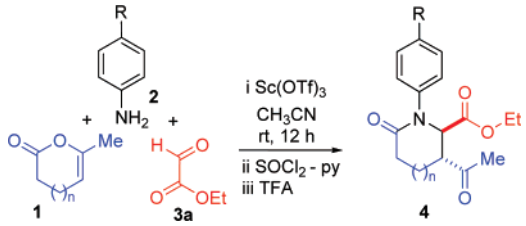
(16) Quinoline **5b** has previously been described: Alves, M. J.; Azoia, N. G.; Gil Fortes, A. *Tetrahedron* **2007**, *63*, 727.

(17) See, for instance: Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009.

(18) For a related transformation involving the more reactive *N*-acyliminium ions, see: (a) Katritzky, A. R.; Ignatchenko, A. V.; Lang, H. *J. Org. Chem.* **1995**, *60*, 4002. (b) Meester, W. J. N.; van Maarseveen, J. H.; Kirchsteiger, K.; Hermkens, P. H. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Arkivoc* **2004**, 122.

(19) In this case, the stereochemical complexity of the resulting double lactam was simplified by the acid-catalyzed isomerization to yield a major trans−trans stereoisomer of unknown relative stereochemistry.

Table 2. Range of Anilines Evaluated for Lactam Formation



entry	R	n	compd	yield[a] (%)
1	4-Me	1	**4a**	40
2	4-Me	0	**4b**	31
3	4-OMe	1	**4c**	35
4	4-OMe	0	**4d**	28
5	4-Br	1	**4e**	26
6	4-Br	0	**4f**	25
7	4-Cl	0	**4g**	24
8	4-CO_2Et	1	**4h**	45
9	3-NO_2	1	**4i**	40
10	2-NO_2	0	**4j**	11

[a] Isolated yield of diastereomeric mixture (1:9 cis/trans) after one-pot MCR−recyclization−epimerization.

considerably less reactive than enol ethers and *O*-silyl activated olefins,[20] enol esters are attractive reagents due to their availability, stability, and versatility. The synthetic outcome of these processes includes simple Mannich reactions (isopropenyl acetate), quinoline synthesis (vinyl acetate), and more interestingly, a new straightforward stereocontrolled access to *N*-arylated lactams (cyclic enol esters **1a** and **1b**). It should be mentioned that this scaffold, widely reported in the literature,[21] displays relevant bioactivity[22] and was not previously available through MCRs. Additional experimentation is underway to optimize the process and to further expand the use of different enol esters in MCRs.

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Supporting Information Available: Experimental procedures, spectral data, copies of the ^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic data of compound **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For a recent result, see: Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507.

(21) Approximately 150 000 substances with a 5- or 6-membered ring *N*-aryl lactam core are listed in *SciFinder* (2006).

(22) For recent results, see: (a) Mitchell, G.; Barnes, N.; Cox, J. M.; Mathews, I. R.; Parry, D. R.; Pearson, D. P. J.; Smith, S. C. *Synthesis and Chemistry of Agrochemicals*; ACS Symposium Series VI; American Chemical Society: Washington, DC, 2002; 800, ppp 18−29. (b) Xi, N.; Arvedson, S.; Eisenberg, S.; Han, N.; Handley, M.; Huang, L.; Huang, Q.; Kiselyov, A.; Liu, Q.; Lu, Y.; Nunez, G.; Osslund, T.; Powers, D.; Tasker, A. S.; Wang, L.; Xiang, T.; Xu, S.; Zhang, J.; Zhu, J.; Kendall, R.; Dominguez, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2905.