Multicomponent Reactions

DOI: 10.1002/ange.201202927

Exploration of Forbidden Povarov Processes as a Source of Unexpected Reactivity: A Multicomponent Mannich–Ritter Transformation**

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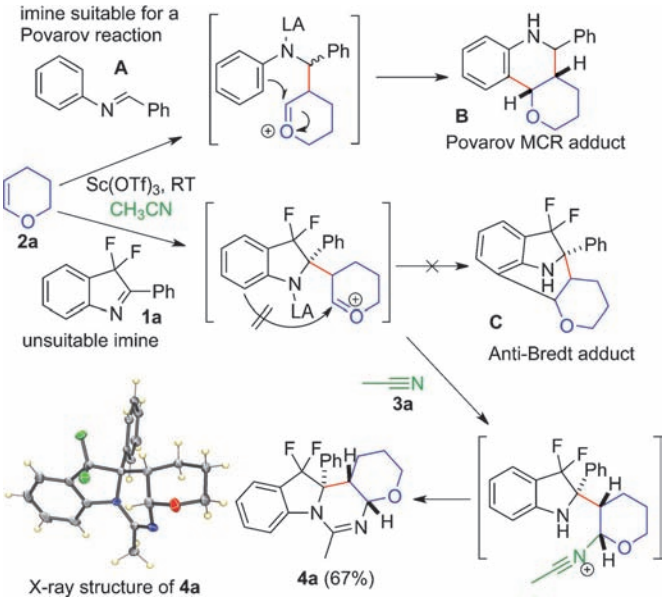
The ideal synthesis constitutes the ultimate challenge in organic transformations.[1] In this context, multicomponent reactions (MCRs) have enormous conceptual and practical advantages,[2] especially for the exploitation of molecular diversity based on heterocycles,[3] as these substructures are widely present in natural products, bioactive compounds, and drugs. This is exemplified by the Povarov reaction,[4] which provides highly convenient access to the ubiquitous tetrahydroquinoline scaffold. This transformation features the interaction of an aniline, a carbonyl compound, and an electron-rich olefin (under acid catalysis) to generate the MCR adduct **B** through the intermediacy of an imine **A** (Scheme 1).[5,6] In this process, the olefin should be amenable to bond formation with the imine carbon and one unsubstituted *ortho* position of the aniline ring (Scheme 1). We report here the results of exploratory chemistry we carried out on systems in which this pathway is geometrically or electronically infeasible.[7]

The cyclic imine **1a**[8] was reacted with 2*H*-dihydropyran (**2a**) under standard conditions with $Sc(OTf)_3$ catalysis[9] in acetonitrile (**3a**) at room temperature. The Povarov product (**C**, Scheme 1) was not formed as it would feature a highly strained anti-Bredt moiety.[10] Instead, the Mannich process was followed by a sequential Ritter step and completed by amidine formation through trapping of the nitrilium ion by the aniline nitrogen,[11] yielding the three-component-reaction adduct **4a** (67%) in a stereoselective manner (Scheme 1). The structure of **4a** was unequivocally determined by X-ray structure analysis.[12] The stereochemical features of this product reflect the expected patterns of interaction between



Scheme 1. Suitable and unsuitable imines for Povarov MCRs. L.A. = Lewis acid.

the two π systems to generate a C–C bond,[4–6] followed by the nitrile addition to the cyclic oxocarbenium ion to yield a *cis*-fused pyran ring.[13] This finding sparked a series of experiments to determine the usefulness of the new reaction. Its scope was investigated by systematically scanning all the components.

α-Substituted difluorinated indolenines **1b–d** afforded the corresponding adducts **4b–d** (Table 1, entries 1–4). The carbonyl analogue **1e** was also productive (Table 1, entry 5), whereas the dimethylindolenine **1f** (entry 6) failed to react, probably because of steric hindrance or lack of activation. Interestingly, the N- and O-heterocyclic derivatives **1g** and **1h** (Table 1, entries 7 and 8) yielded **4g** and **4h**, respectively, the latter being isolated after MeOH quenching. However, the phenyl-substituted derivative **1i** gave only traces of the MCR adduct. In these reactions, *N*-alkylimines were almost unreactive.[14] Analogous restrictions were found for *o*,*o*′-disubstituted aromatic imines such as **1j** (Table 1, entry 9). The latter substrates did not undergo the Mannich–Ritter process, except in trace amounts, reflecting the practical limits of the reaction. In contrast, the highly electrophilic *m*-dinitroaniline derivative afforded the *trans* tetrahydropyran **4k** (16% unoptimized yield; Table 1, entry 10), presumably after spontaneous epimerization. This is a remarkable example of

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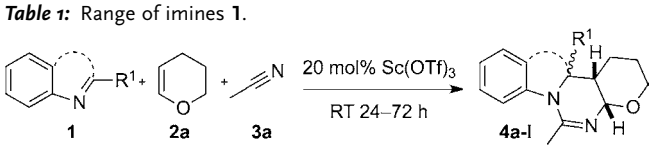
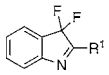
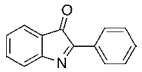
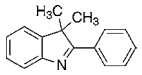
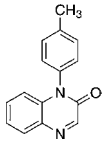
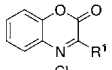
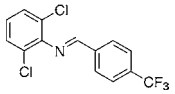
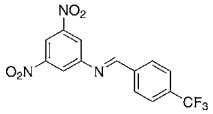
[**] This work was supported by DGICYT—Spain (projects BQUCTQ2009-07758 and SAF2011-27642), Generalitat de Catalunya (projects 2009SGR 1024 and 298), CESCA, and Grupo Ferrer (Barcelona, Spain).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202927.

Table 1: Range of imines **1**.



1 **2a** **3a** **4a-l**

Entry[a]	Imine	1	Yield [%][b]	Prod.
1		**1a**, R^1 = Ph	67[c]	**4a**
2		**1b**, R^1 = 4-OMe-C_6H_4	32[c]	**4b**
3		**1c**, R^1 = 3,4-$(MeO)_2$-C_6H_3	25[c]	**4c**
4		**1d**, R^1 = CO_2Et	44	**4d**
5		**1e**	60	**4e**
6		**1f**	–	–
7		**1g**	63	**4g**
8		**1h**, R^1 = H	26[d]	**4h**
		1i, R^1 = Ph	traces[e]	**4i**
9		**1j**	traces[e]	**4j**
10		**1k**	16	**4k**

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3a** (excess), $Sc(OTf)_3$ (0.20 mmol), RT, 24–72 h, Ar. [b] Yields of isolated products. Isomer ratio > 96:4. [c] Traces of the carbonyl analogue of the final adduct were detected, which formed by hydrolysis of the starting difluorinated imine. [d] After MeOH quenching. [e] Stereochemistry not assigned.

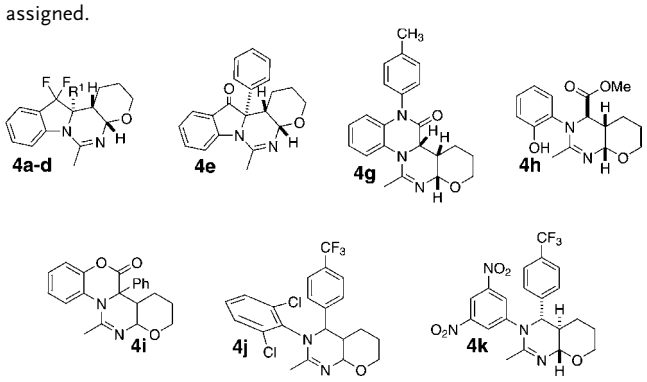
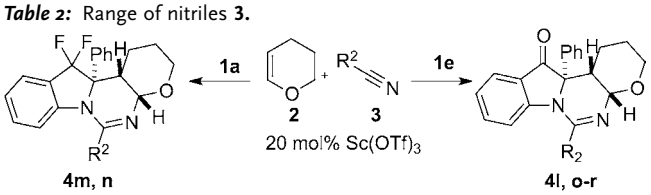
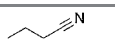
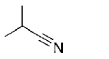
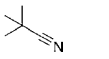
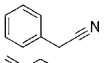
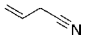
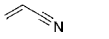
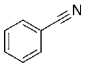
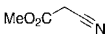


Table 2: Range of nitriles **3**.



4m, n **2** **3** **4l, o-r**

Entry[a]	Imine	Nitrile	3	Yield[%][b]	4
1	**1e**		**3b**	69	**4l**, R^2 = Pr
2	**1a**		**3c**	59	**4m**, R^2 = *i*Pr
3	**1a**		**3d**	–	–
4	**1a**		**3e**	40	**4n**, R^2 = Bn
5	**1e**		**3f**	41	**4o**, R^2 = (*E*)-1-propenyl
6	**1e**		**3g**	53	**4p**, R^2 = vinyl
7	**1e**		**3h**	44	**4q**, R^2 = Ph
8	**1e**		**3i**	49[c]	**4r**, R^2 = 2-hydroxy-2-methoxyvinyl

[a] See footnote [a] in Table 1. [b] Yields of isolated products. [c] A stoichiometric amount of **3i** was used and **3d** served as the solvent.

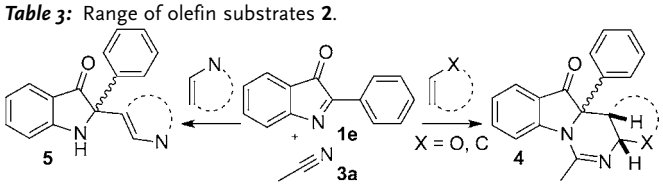
the new MCR, which may formally give rise to standard Povarov adducts, owing to the free *ortho* positions on the aniline precursor.

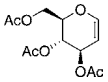
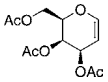
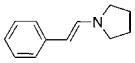
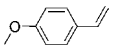
The range of nitriles was studied next using imines **1a** and **1e** as probes, and enol ether **2a** as the olefin component (Table 2). In addition to acetonitrile **3a** (Table 1, entry 1), linear, branched alkyl, benzyl, and allyl cyanides worked very well (Table 2, entries 1, 2, 4, and 5), although the latter adduct presumably isomerized afterwards under acid catalysis to the conjugated amidine **4o**. On the other hand, *tert*-butylcyanide (**3d**) was completely unreactive (Table 2, entry 3). Acrylo- and benzonitrile were suitable substrates for these transformations (Table 2, entries 6 and 7). A functionalized nitrile such as methyl cyanoacetate (**3i**) afforded the corresponding MCR product (**4r**; Table 2, entry 8) isolated as the enol tautomer. The main restriction in this process is the requirement of a large excess of nitrile **3**.[11,15] However, when the "inert" *tert*-butylcyanide served as the solvent it was possible to use only one equivalent of the desired nitrile to achieve comparable yields (Table 2, entry 8). This is particularly interesting, since the most useful catalyst, $Sc(OTf)_3$, performs best in nitrile solvents.[16,17]

Once the range of imines and nitriles was defined, attention was focused on the activated olefin component. Distinct types of enol ethers (Table 3, entries 1–4) afforded the MCR adducts under modified reaction conditions. Thus, 2,3-dihydrofuran (**2b**) and glucal **2c** reacted at higher temperatures, whereas galactal **2d** required microwave irradiation. The reaction with vinyl acetate (**2e**) yielded the hydrolyzed MCR product (**4v**) after chromatographic purification. In the case of N-activated olefins (Table 3, entries 5–8), the main product arose from a Mannich interaction, in sharp contrast with the outcome observed in standard Povarov reactions.[18] In this way, the unsaturated lactam **2f** afforded adduct **5a**. Analogously, enamide **2g** and thiazolone **2h** (Table 3, entries 6 and 7) yielded **5b** and **5c**, respectively, whereas enamine **2i** gave, after the addition process, the hydrolyzed aldehyde **5d** (entry 8). Conjugated olefins such as styrene **2j** (Table 3, entry 9) yielded the expected adduct as a 4:5 mixture of stereoisomers.

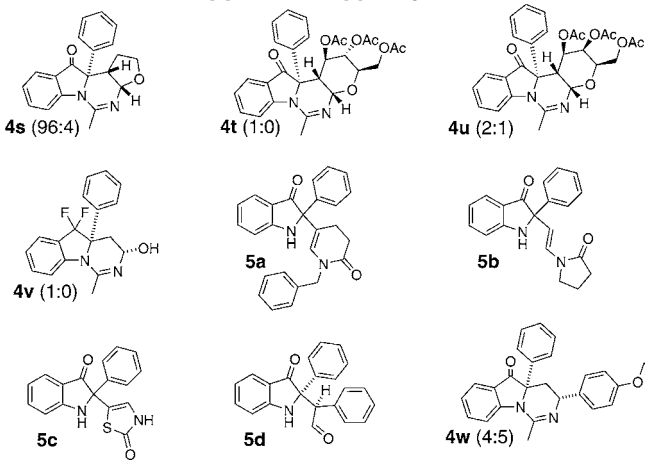
Finally, under standard conditions the sterically hindered imine **1l** afforded the 4-quinolone adduct **6** together with fluoropyridine **7** (Scheme 2). The former compound was

Table 3: Range of olefin substrates **2**.



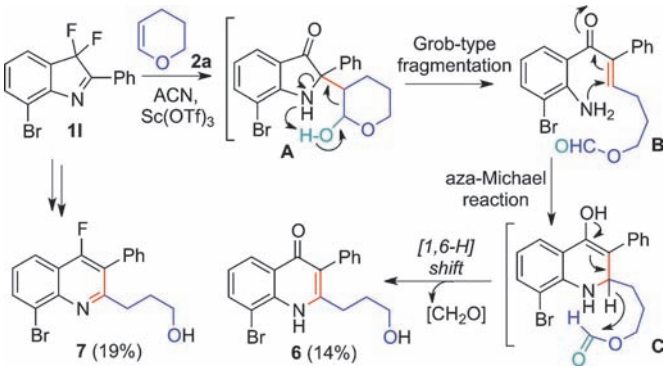
Entry[a]	Olefin substr.	2	Yield [%][b]	Product
1		**2b**	38	**4s**
2		**2c**	17	**4t**[c]
3		**2d**	47	**4u**[d]
4		**2e**	49	**4v**[e]
5		**2f**	64	**5a**
6		**2g**	21	**5b**
7		**2h**	59	**5c**
8		**2i**	49	**5d**
9		**2j**	25	**4w**

[a] See footnote [a] in Table 1. [b] Yields of isolated products. [c] 10 min, 80 °C, MW irradiation. [d] 60 °C, 12 h. [e] Using **1a** as the imine.



unequivocally identified by X-ray structure analysis.[12] The quinolone derivative[19] may arise from a complex sequence involving a Grob-type fragmentation,[20] an aza-Michael process, and a 1,6-hydride shift[21] with concomitant elimination of a formaldehyde equivalent. The fluoropyridine **7** was produced in an analogous manner. This represents a very unusual outcome in a Mannich process involving a cyclic enol ether, where its α-carbon is lost, leading to a substituted quinolone.

Since the nature of the olefin plays a major role in determining the outcome of Povarov MCRs, quantum mechanical computations (MP2/aug-cc-pVDZ; see the Supporting Information) were carried out to examine the energetics for the addition of acetonitrile to the carbenium



Scheme 2. New pathways for hindered imine **1l**.

intermediate generated upon C–C bond formation with indolenine **1e**. Calculations were performed for two olefins that behave in different ways: dihydropyran (**2a**) (which yielded 60% MCR adduct) and cyclic enamide **2f** (0%). Owing to the large size of the intermediate, computations were performed using a mimic where the bound cyclic imine was replaced by a methyl group. The energy profiles indicate that the attack of acetonitrile *cis* to the methyl group is the preferred route, as expected from the greater stability of the chairlike transition state (TS) compared to the boatlike TS formed by *trans* addition (Figure 1).[13] The absence of the MCR adduct for enamide **2f** is explained by the higher

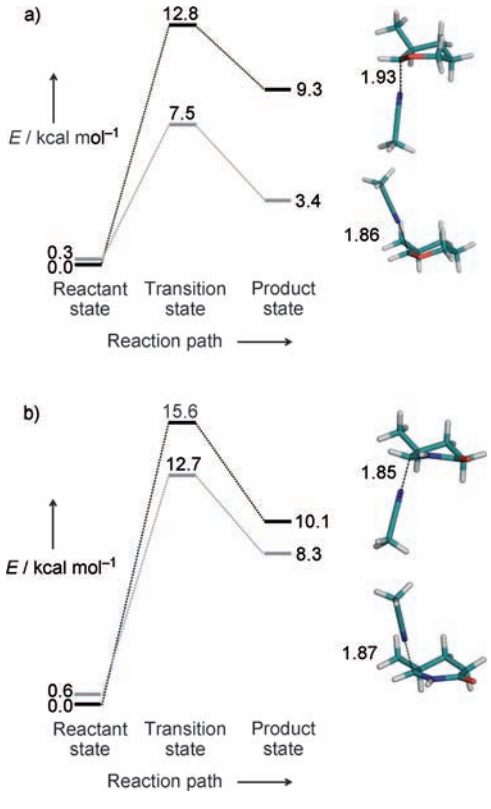


Figure 1. Energy profile (kcal mol^{-1}) for the *cis* (gray) and *trans* (black) addition of acetonitrile to the carbenium intermediate formed from dihydropyran **2a** (a) and cyclic enamide **2f** (b), and representation of the chair- and boatlike transition states formed in the *cis* and *trans* additions (the length of the forming bond is given in Å).

barrier of the *cis* addition (12.7 kcal mol^{-1}) compared to that for **2a** (7.5 kcal mol^{-1}), which can be attributed to the greater conformational strain introduced by the planarity of the amide group in the chairlike TS (Figure S1 in the Supporting Information).

In conclusion, the use of restricted imines in Povarov-type processes has led to the discovery of a new MCR providing cyclic amidines. This finding is complemented by the description of alternative pathways for the formation of these complex systems, including the production of Mannich and interrupted Povarov adducts. The new reaction involves three different inputs, three bonds are formed in a stereoselective manner, and complex and diverse products are produced in competitive yields. The different synthetic outcomes mainly reflect the balance of the reactivity and torsional strain of the olefins. Overall, the results indicate that the systematic exploration of uncharted reactivity space related to formally forbidden processes can be useful in the search for new MCRs, since a blocked step may enable unexpected bond-formation events within the same reactant mixture.[22]

Received: April 17, 2012
Published online: May 31, 2012

Keywords: domino reactions · heterocycles · multicomponent reactions · Ritter reaction · Schiff bases

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