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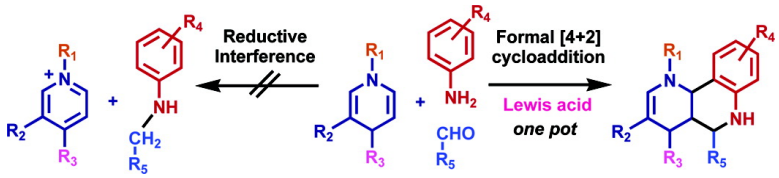

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Multicomponent Reactions with Dihydroazines: Efficient Synthesis of a Diverse Set of Pyrido-Fused Tetrahydroquinolines

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A multicomponent assembly of pyrido-fused tetrahydroquinolines is accomplished in a one-pot process from the interaction of dihydroazines, aldehydes, and anilines. A rational screening of the different components and parameters of this reaction, such as the range of reactive starting materials, catalysts and reaction conditions (solvent range; thermal, high pressure- and microwave-promoted processes) is carried out. Optimized conditions allow an efficient preparation of pyrido-fused tetrahydroquinolines with good yields, bypassing the biomimetic NADH-like reductive pathway which is typical in the interaction of dihydropyridines with carbonyl compounds and amines. Furthermore, solid-supported versions of the process have been developed, which should facilitate the preparation of libraries.

Introduction

One of the main challenges of organic synthesis is to develop suitable synthetic access to the broad variety of structural types found in carbogenic compounds. Impressive progress has been achieved in areas of selectivity control, connectivity, synthesis design, catalysis, etc.[1] However, other factors, such as versatility, parallelization, and efficiency, are playing an increasingly important role in medicinal chemistry.[2] Diversity-oriented synthesis (DOS) has recently emerged as a new tool in the study of the chemistry/biology interface, and exciting results have been reported using this approach to discover novel bioactive small-molecule compounds.[3] In these fields, the presence of heterocyclic cores is directly linked to bioactivity, and such motifs are frequently found in "privileged structures".[4] Therefore, the methodology for the incorporation of heterocyclic rings, especially those that contain nitrogen,[5] into complex molecules is scientifically relevant. This fact is even more significant when multicomponent reactions (MCRs) are involved, because this kind of process allows the introduction of a high degree of molecular diversity in just a single step.[6] Herein, a novel MCR incorporating dihydropyridines (DHPs)[7] is reported. The use of DHPs in MCRs is especially appealing since they are readily available from pyridinium salts and display a high degree of substitution; their reactivity is quite general and allows many synthetically relevant transformations; and finally, they can be considered as natural precursors to interesting piperidine-based scaffolds, including those showing unusual substitution patterns (Figure 1). On the other hand, a potential drawback of their synthetic utility is their tendency to oxidize to the corresponding pyridinium salts.

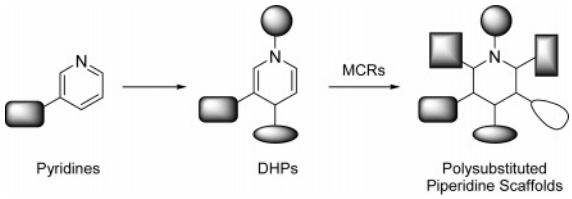

Figure 1. Synthetic strategy for the functionalization of pyridines.

In fact, nature's role for NADH (a 1,4-dihydropyridine) is to promote the reduction of imines and carbonyl compounds (becoming oxidized to NAD^+ in the event). However, we have recently shown that it is feasible to avoid this oxidative fate and, in what we term *nonbiomimetic transformations*, we have achieved alternative oxidative routes by bonding DHPs with electronegative atoms in chemically productive processes.[8]

Results

In this context, we were interested in the development of the MCR strategy in aza-Diels−Alder-type reactions, in which the enamine moiety of the DHP could be considered as the electron-rich dienophile, and the aryl imine (the *formal* azadiene partner) was to be formed through the interaction of an aniline and a carbonyl compound.[9] This multicomponent assembly of a tetrahydroquinoline system (an important scaffold with a wide range of biological activities)[10] has been successfully exploited in several synthetic approaches, allowing the preparation of diversely substituted derivatives and even complex natural products.[11]

On the basis of this idea, the reaction between DHPs (as electron-rich olefins) and imines in acid-catalyzed cycloadditions was first examined. Accordingly, the three-component interaction of an *N*-alkyl-1,4-DHP (**1**) with an aniline (**2**) and an aldehyde (**3**) was screened. This would lead (through the in situ formation of the corresponding imine) to the

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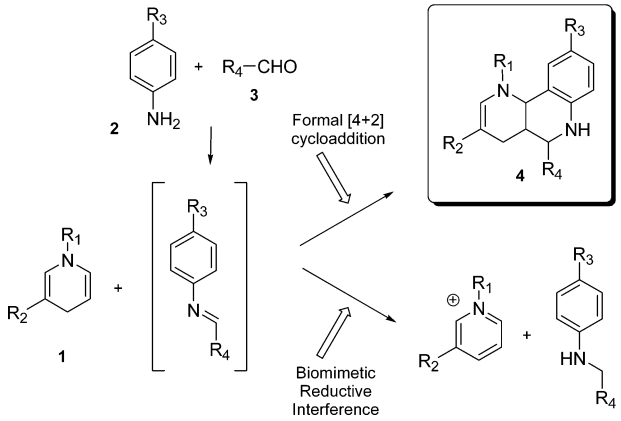
Scheme 1. Biomimetic and Nonbiomimetic Reactive Pathways of Dihydropyridines



benzonaphthyridine-type adduct **4** (the parent heterocyclic system is also very frequently found in bioactive compounds), in a formal [4 + 2] cycloaddition. It should be remarked that the process, although well precedented for olefins, enol ethers, and enamines, presents here the possibility of a reductive capture of the imine intermediate by the NADH analogue **1**, leading to the pyridinium salt and the corresponding secondary amine (Scheme 1).

Catalyst Screening. A systematic study of a model reaction between DHP **1a**,[12] *p*-methylaniline (**2a**) and ethyl glyoxylate (**3a**) was undertaken.[13] Although almost any acid catalyst promotes the imino-Diels−Alder process, in this case, the reactivity was dramatically dependent on the catalyst used. The initial screening included protic[14] and aprotic[15] sources [TFA, $BF_3{\cdot}Et_2O$ and $Mg(ClO_4)_2$] which failed to generate the desired cycloadduct. The first two acids polymerized the starting DHP, whereas the third acid efficiently promoted the biomimetic hydride transfer to yield the reduced amine and the pyridinium salt. However, the use of $InCl_3$[16] and $Sc(OTf)_3$[17] reversed this selectivity, affording the expected compounds with only residual contamination from the redox products. Interestingly, Sc(III) salts have been used for promoting reductive aminations using Hantzsch DHPs,[18] although they have also promoted [3 + 2] cycloadditions with NADH-like DHPs.[19] The reactions were conducted at room temperature with 20% mol equiv of the catalyst in dry CH_3CN in the presence of 4-Å molecular sieves and afforded a 2:1 mixture of the desired tricyclic compounds **4a**−**a′** in 65% overall yield [$InCl_3$] and 70% $Sc(OTf)_3$. The diastereomeric mixtures were conveniently separated by flash chromatography on silica gel (Scheme 2).[20] A reasonable explanation for the success of this reaction may involve a kinetic competition between the redox and the bond-forming processes, the latter being the most favored by these Lewis acid catalysts.

Scheme 2. MCR-Based Synthesis of Compounds **4a**−**a′**

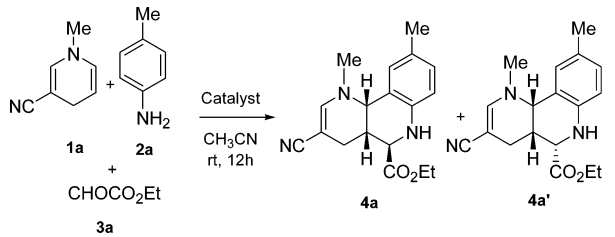


Table 1. Yields of Cycloadducts **4a**−**a′** Obtained with Different Catalysts

entry	acid catalyst	yield (%)
1	TFA	*a*
2	$BF_3{\cdot}Et_2O$	*a*
3	$Mg(ClO_4)_2$	*a*
4	$InCl_3$	65
5	$Sc(OTf)_3$	70
6	$Sn(OTf)_2$	67
7	$Y(OTf)_3$	76
8	$Yb(OTf)_3$	85
9	$Pb(CF_3CO_2)_2$	72
10	$Cu(OTf)_2$	64
11	$Ce(OTf)_3$	86

[a] Not detected.

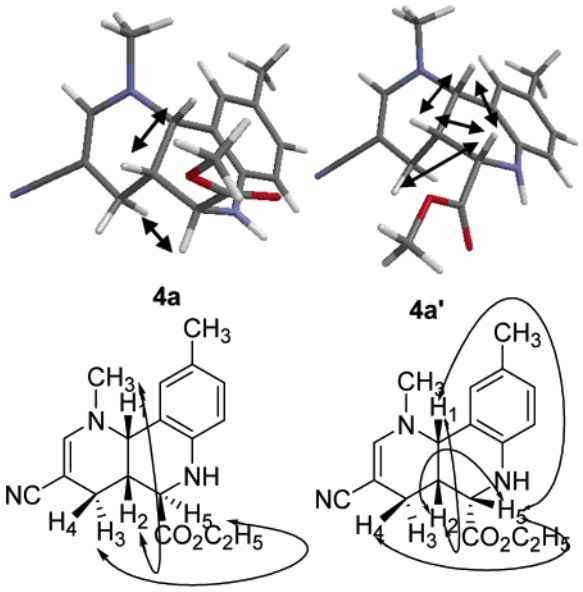


Figure 2. Optimized geometries (MMF94 and AM1) and diagnostic NOEs in **4a** and **4a′** (the models are represented as methyl esters for clarity).

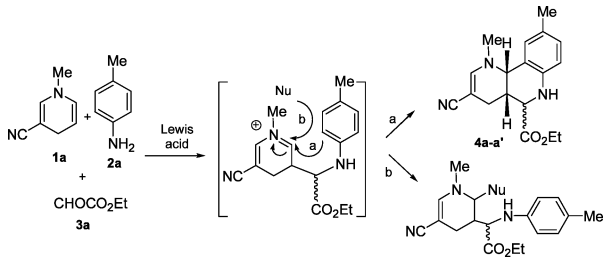
The recently described lanthanide Lewis acids, whose properties seem to be ideal for the requirements of MCRs, were subsequently tested. In particular, it was important to take advantage of their N versus O selectivity, their compatibility with aqueous environments, and the possibility of tuning the reactivity with ligands.[21] The process was scrutinized for the most widely used catalyst, and the yields and stereoselectivities were analyzed by ^1H NMR (Table 1). Although the overall yields were acceptable, ranging from 63 to 86%, the stereoselectivity remained practically unchanged, affording only modest diastereomeric excesses (with the ratio of **4a**/**4a′** being 2:1 in almost all cases).[22] The lack of selectivity may be balanced by the fact that the access to both stereochemistries is granted.

Structural Elucidation/Mechanistic Implications. The structural assignment of compounds **4a**−**a′** was performed by NMR experiments (^1H, ^{13}C, NOESY, COSY, HSQC). The cis fusion in the naphthyridine moiety was confirmed by the vicinal coupling constant between H_1 and H_2 (~4 Hz in both isomers), and the expected NOEs between H_1 and H_2 (Figure 2). Furthermore, the relative stereochemistry of the ester α position was determined with the NOEs between

H_3 and H_5 in **4a** and between H_1 and H_5, and H_2 and H_5 in **4a′**. The optimized geometries for these compounds, obtained with molecular mechanics (MMF94) and semiempirical (AM1) methods,[23] displayed structural features which matched the observed spectroscopic data. The models show a flexible tricyclic arrangement, in agreement with the cis fusion. Interestingly, the models display their substituents pointing in different directions, with practically no steric interferences among them, an especially important property for scaffolds in medicinal chemistry. Although the calculated heat of formation for the two isomers differed by ~0.6 kcal mol^{-1}, the attempted epimerization between the two isomers under basic catalysis was not successful under the conditions tested (*tert*-BuOK, EtOH).

The mechanism of the aforementioned formal [4 + 2] cycloaddition is believed to occur in a stepwise manner,[24] the first step being the electrophilic interaction of the DHP with the in situ formed imine (probably activated by coordination with the Lewis acid), to form an iminium ion, which would then undergo an intramolecular attack by the aryl group of the aniline moiety to induce the ring closure preferentially in a syn mode, leading to a cis stereochemistry at the ring fusion. Interestingly, the trapping of this intermediate by different nucleophilic species (terminators) would give rise to new structural motifs.[24d] (Scheme 3).

Scheme 3. Stepwise Mechanism of the MCR



Survey of Reaction Conditions. The effect of the solvent used on the outcome of the reaction was first studied, starting with CH_3CN (Table 2, entries 1 and 2). THF and CH_2Cl_2 (entries 3 and 4) were ineffective, because the desired cycloadduct was not detected under the usual reaction conditions. However, when using mixtures of these solvents containing significant amounts of CH_3CN, the process was again productive. Interestingly, no loss of yield was observed when the process was carried out in the absence of molecular sieves. The possibility of performing MCRs in water offers several advantages, including the benefits of green procedures and, in some cases, improved kinetics.[25] On the other hand, the Lewis acids used here are also active in aqueous media, and the solubility of organic substrates in water was dramatically increased using sodium dodecyl sulfate (SDS) as a surfactant to form anionic micelles that hold in their external surfaces the cationic Lewis acid.[26,21b] Under such conditions, the desired products **4a**−**a′** [$InCl_3$ (56%, 1:1) and $Sc(OTf)_3$ (72%, 1:1)] were obtained (entries 5 and 6). Next, the effect of high pressure (13 kbar) in the formal cycloaddition was studied, resulting in a very clean reaction (97%) with a clear reversal of the stereoselectivity, now favoring the **4a′** isomer (entry 7).[27,28] The process was also greatly accelerated under microwave irradiation.[29] Thus, in only 5 min at 80 °C and 100 W an isolated yield of 80% was obtained (the reaction takes ~12 h at room temperature under conventional thermal activation). In this case, no changes in the selectivity were noticed (entries 8 and 9). Finally, a polymer-bound Lewis acid [ytterbium (III) polystyrylsulfonate] was shown to be an efficient and recoverable catalyst. Thus, the desired compounds **4a**−**a′** were obtained in 89% yield (entry 10). Interestingly, after the polymer was washed and the process was repeated, the second, third, and fourth runs using the recovered catalyst afforded yields and purities similar to those obtained in the first run.[30]

Table 2. Survey of Reaction Conditions

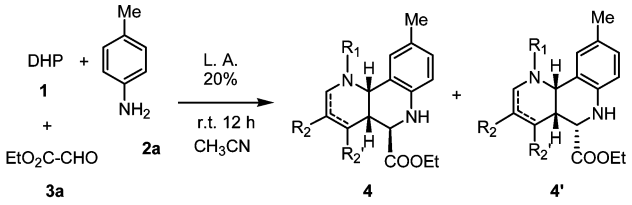
entry	conditions	solvent	Lewis acid	yield (%)
1	rt, 12 h	CH_3CN	$InCl_3$	65
2	rt, 12 h	CH_3CN	$Sc(OTf)_3$	70
3	rt, 12 h	CH_2Cl_2	$InCl_3$	*b*
4	rt, 12 h	THF	$InCl_3$	*b*
5	rt, 12 h	H_2O/SDS	$InCl_3$	56
6	rt, 12 h	H_2O/SDS	$Sc(OTf)_3$	72
7	HP, 13 kbar	CH_3CN	$Sc(OTf)_3$	97
8	MW, 25 w, 20 min	CH_3CN	$Sc(OTf)_3$	74
9	MW, 100 w, 5 min	CH_3CN	$Sc(OTf)_3$	80
10	rt, 12 h	CH_3CN	Yb(III)[a]	89

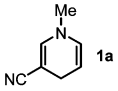
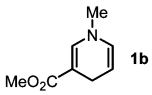
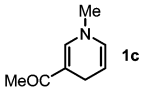
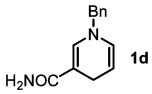
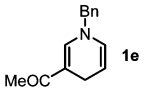
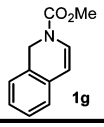
[a] Polymer-bound. [b] Not detected.

Survey of Reactants. Variation of the DHP Component. As expected, the reaction works well with different substituents attached to the nitrogen (Me and Bn) and with the typical electron-withdrawing groups linked to the β-position of the ring, required for the stability of the DHP ring (CN, CO_2Me, COMe, $CONH_2$) (Table 3, entries 1−7). It should be noted again that the yields obtained with Sc(III) were consistently ~10% higher than those found with In(III). The use of *N*-acyldihydroazines would increase the structural diversity of the process; for this reason, the reactivity of the *N*-methoxycarbonyl-1,2-dihydropyridine (**1f**) was examined. Hence, naphthyridine **4f** [37%, $Sc(OTf)_3$] was obtained as a single stereoisomer (entry 8), whereas the corresponding isoquinoline derivative **1g** affords the benzo-analogues **4g**−**g′** [63%, 4:1] (entry 9).

The in situ formation of DHPs by $Na_2S_2O_4$ reduction of the pyridinium salts was considered, but no useful protocols could be developed, partially by the restriction in the use of CH_3CN as the solvent. In a series of related experiments, we explored the introduction of an additional substituent at the DHP γ-position by sequentially carrying a regioselective nucleophilic addition to a pyridinium salt, with the generation of the reactive DHP which, in a tandem process, will react with ethyl glyoxylate and the *p*-alkylaniline (Scheme 4). In this way, successful one-pot processes allowing the incorporation of cyano, phosphonate, and aminouracil residues were developed, and the corresponding products **5a**−**a′**, **5b**−**b′**, and **5c**−**c′** were prepared as the usual diastereomeric mixtures at the α-ester position, thus controlling the relative configuration of three of the four centers. The stereochemical outcome can be rationalized by considering the preferential attack of the dihydropyridine ring upon the iminium ion taking place from its less substituted face.[31]

Table 3. Range of DHPs **1** in the MCR Process



Entry	DHP	Lewis acid	Product	Yield (%)
1	 **1a**	$InCl_3$	**4a-a'**	65
2		$Sc(OTf)_3$		70
3	 **1b**	$InCl_3$	**4b-b'**	63
4		$Sc(OTf)_3$		86
5	 **1c**	$InCl_3$	**4c-c'**	56
6	 **1d**	$Sc(OTf)_3$	**4d-d'**	67
7	 **1e**	$Sc(OTf)_3$	**4e-e'**	86
8	 **1f**	$Sc(OTf)_3$	**4f**	37
9	 **1g**	$Sc(OTf)_3$	**4g-g'**	63

Variation of the Aniline Component. The goal in this set of experiments was to determine the practical limits of the reaction with respect to this diversity element and, taking into account the reaction mechanism, to explore the influence of the substitution at the aromatic ring on the final cyclization step (see Table 4). A series of MCRs was performed under standard conditions using a parallel reactor. No optimization of any individual process was considered, and the compounds of this chemset were positively identified by ^1H NMR or HPLC/MS techniques. As expected, mild activating and deactivating groups allowed the reaction (alkyls and halides, entries 1, 2, 4, and 5). For unknown reasons, aniline failed to yield significant amounts of the expected compounds (entry 3). Activating substituents, such as acetoxy, hydroxy, and acetamido groups (entries 6, 7, and 9), afforded the desired compounds, but the strongly activated *m*-methoxyaniline (entry 8) failed to do so, and the reaction progressed with exclusive addition of the aniline to the intermediate imine.[32] With deactivating groups such as carboxylate (as the tetrabutylammonium salt), carboxamido, and methoxycarbonyl, the reaction was feasible, although somewhat slower and with moderate or low yields (entries 10−12). In agreement with the proposed mechanism, strongly deactivated nitroanilines (entries 13−14) completely failed to provide the cyclized compounds **4**.

Scheme 4. MCRs with In Situ-Formed DHPs

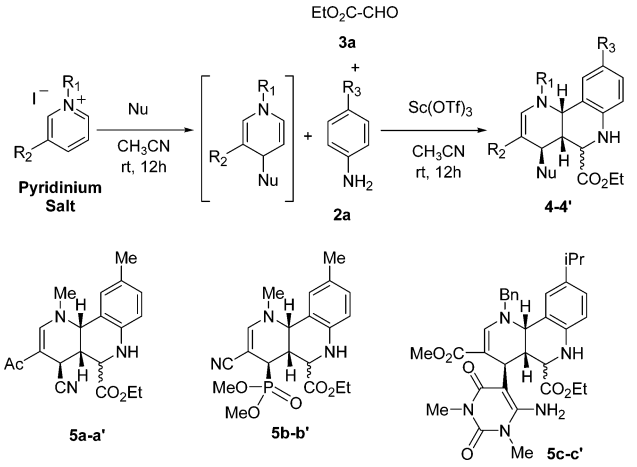
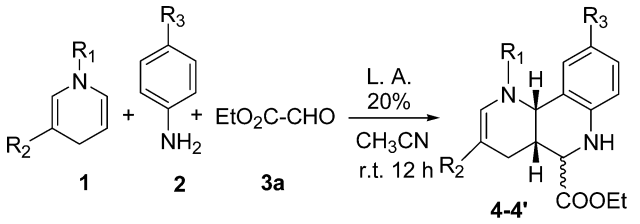


Table 4. Range of Anilines in MCRs

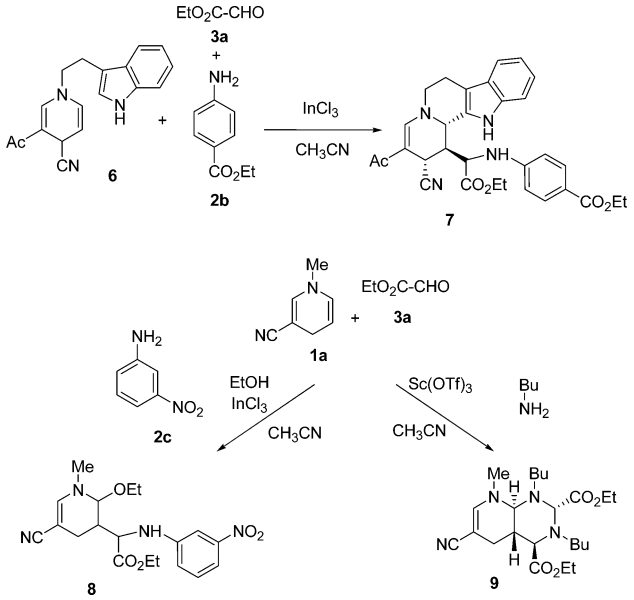


entry	R_1/R_2	R_3	Lewis acid	product	yield (%)
1	Me/CN	Me	$InCl_3$	**4a−a′**	65
2	Me/CN	*i*-Pr	$Y(OTf)_3$	**4h−h′**	54
3	Me/CN	H	$Sc(OTf)_3$		*b*
4	Me/CO_2Me	Br	$Sc(OTf)_3$	**4i−i′**	68
5	Bn/COMe	F	$Y(OTf)_3$	**4j−j′**	16
6	Me/CO_2Me	OAc	$Sc(OTf)_3$	**4k−k′**	70
7	Me/CO_2Me	*o*-OH	$Y(OTf)_3$	**4l−l′**	65
8	Me/CN	*m*-OMe	$Sc(OTf)_3$		*b*
9	Me/COMe	NHAc	$Y(OTf)_3$	**4m−m′**	65
10	Me/CN	CO_2NBu_4	$Y(OTf)_3$	**4n−n′**	24[a]
11	Me/CN	$CONH_2$	$Y(OTf)_3$	**4o−o′**	22
12	Me/CN	CO_2Et	Sc $(OTf)_3$	**4p−p′**	15
13	Me/CN	*o*-NO_2	$Y(OTf)_3$		*b*
14	Me/CN	*m*-NO_2	$Sc(OTf)_3$		*b*

[a] Isolated as the ethyl ester derivative after acid-catalyzed esterification. [b] Not detected.

The reduced ability of deactivated anilines to promote the final cyclization opens the possibility of alternative trappings for the iminium ion intermediate. Thus, interaction with an internal nucleophile was explored using a suitably located indole ring in the tryptophylDHP (**6**), which reacted with ethyl glyoxylate (**3a**) and ethyl *p*-aminobenzoate (**2b**, Scheme 5). In this way, the indoloquinolizidine **7** derivative was formed (66%, 4:1 mixture of epimers at the α-aminoester

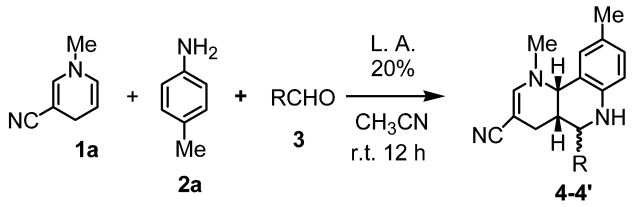
Scheme 5. New Structural Types Derived from the MCR

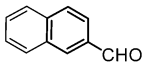
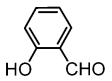
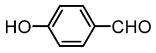
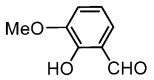
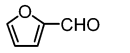
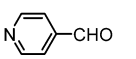


position, stereochemistry not determined) in a stereocontrolled manner. This result was complemented with an example of external nucleophilic trapping, in which the iminium ion is captured by a molecule of EtOH. Hence, DHP **1a**, ethyl glyoxylate (**3a**), *m*-nitroaniline (**2c**), and EtOH afforded the 4CR to form the tetrahydropyridine **8** (54%) as a complex mixture of stereoisomers. In this respect, it should be noted that the participation of different nucleophiles as terminators in these processes is restricted, because they could competitively trap the first iminium generated in the interaction of the aldehyde and the aniline in Strecker-type reactions. However, the reversibility of the interaction with *O*-nucleophiles allows this interesting 4CR to occur. Furthermore, the resulting compound is a known iminium ion precursor and may allow the entry of additional nucleophilic species at the nitrogen α-position in a subsequent step.[33] The participation of *N*-nucleophiles (e.g. alkylamines) follows a modified mechanism, involving addition of the imine, trapping of the iminium ion by a second equivalent of the amine, and a final ring closure by condensation with another molecule of the aldehyde to yield the bicyclic aminal **9** (41%) as a single stereoisomer. Interestingly, the ring fusion shows a trans stereochemistry, probably the result of the more favorable attack of the amine to the iminium ion from its less substituted face, whereas the α-carbonyl centers may be controlled by a thermodynamic equilibration (Scheme 5).[24d] These results truly increase the versatility of the process, allowing the formation of structurally diverse scaffolds using the essentially same chemistry and related starting materials.

Variation of the Aldehyde Component. Different aldehydes were tested in order to determine their influence on the outcome of the MCR. Apart from the highly electrophilic ethyl glyoxylate (**3a**), which was used as a reference, a representative set of aromatic and heteroaromatic aldehydes were considered (Table 5). Acceptable yields were obtained for most of the reagents studied, including rings with electron-donating and electron-withdrawing substituents. Due to the imine-enamine tautomerization, aliphatic aldehydes

Table 5. Effect of Different Aldehydes in the [4 + 2] Process



Entry	Aldehyde (RCHO, **3**)	Lewis acid	Product	Yield (%)
1	EtO_2C–CHO **3a**	$InCl_3$	**4a-a'**	65
2	O_2N–C$_6$H$_4$–CHO	$Y(OTf)_3$	**4q-q'**	67
3	MeO_2C–C$_6$H$_4$–CHO	$Y(OTf)_3$	**4r-r'**	30
4	Cl–C$_6$H$_4$–CHO	$Y(OTf)_3$	**4s-s'**	58[a]
5	C$_6$H$_5$–CHO	$Sc(OTf)_3$	**4t-t'**	20
6		$Y(OTf)_3$	**4u-u'**	9
7		$Y(OTf)_3$	**4v-v'**	40
8		$Y(OTf)_3$	**4w-w'**	20
9		$Y(OTf)_3$	**4x-x'**	17
10		$Y(OTf)_3$	**4y-y'**	70
11		$Y(OTf)_3$	**4z-z'**	63

[a] With DHP **1b**. These reactions afforded the usual 2:1 diastereomeric mixtures, following the same trends as the ethyl glyoxylate processes.

having enolizable hydrogens present special problems in this type of process (they usually generate the Doebner−von Miller condensation products) and until very recently have been excluded from this chemistry.[34] They were not considered in this study. Unfortunately, no reaction was observed in the cases of *p*-formaldehyde, chloral hydrate, and *trans*-cinnamaldehyde.

The interaction of *p*-chlorobenzaldehyde with the less reactive *N*-acylDHP **1f** also produced the desired compounds **4aa**−**aa′** (25%, 1.5:1), although heating for 48h was required (Figure 3). On the other hand, the participation of electrophilic carbonyl derivatives was considered, and in this way, benzoylformate and isatin were reacted with DHP **1a** and *p*-methylaniline (**2a**) under the usual reaction conditions. Although the former did not yield the expected adduct (only the imine and the biomimetic reduction products were detected), the latter afforded the spirocyclic compounds **10a**−

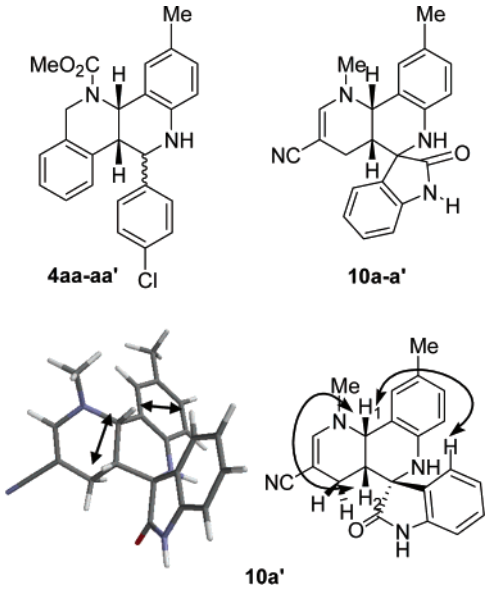


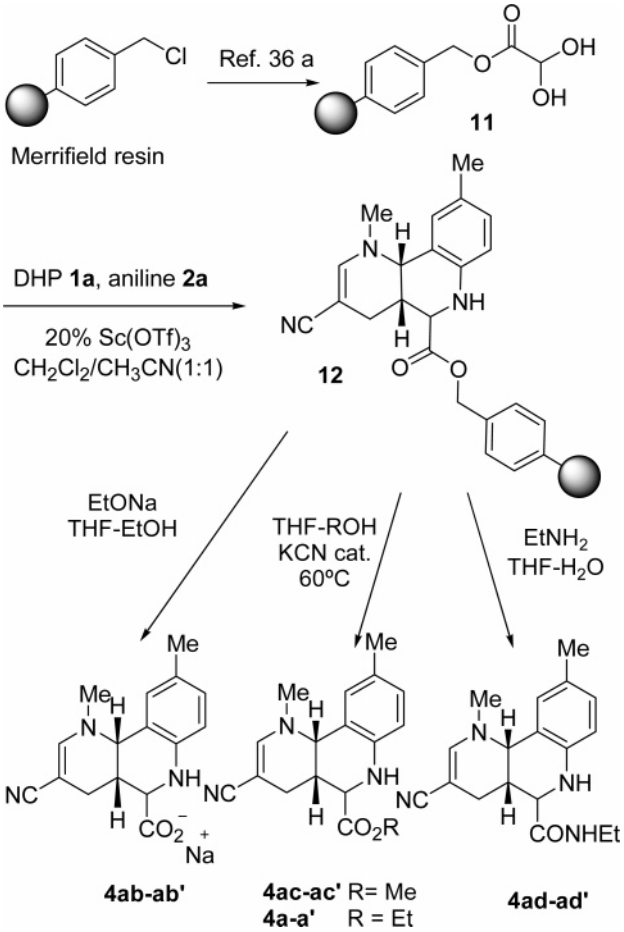
Figure 3. Adducts formed by reaction of DHPs and *p*-methylaniline with *p*-chlorobenzaldehyde and isatin.

a′ in 18% yield (nonoptimized). The major stereoisomer (**10 a′**) was assigned with the aid of NOESY experiments, which showed the diagnostic correlations shown in Figure 3.

Synthesis on Solid Support. The use of solid-phase techniques offers interesting advantages, particularly in the acceleration and parallelization of syntheses, and has been a major breakthrough for the preparation of large collections (libraries) of heterocyclic compounds.[35] Therefore, the possibilities of carrying this MCR under such conditions were examined. Cycloadditions in solid-phase were studied using two complementary approaches: the immobilization of the glyoxylate and also by attaching the aniline component to the solid support. The two most used resins, the Merrifield (benzyl) and the Rink [poly(alkoxybenzylhydrylamine)] resin, have been used for the anchoring of carboxylic moieties. The former is robust, forms an ester bond with the carboxylic acid of the substrate, is stable to TFA, and requires either strong acids such as anhydrous HF or nucleophiles to liberate the final product from the resin. The Rink resin is linked to the substrate via an amide bond, which at the end of the synthesis can be cleaved with TFA, liberating the substrate as an amide.[36]

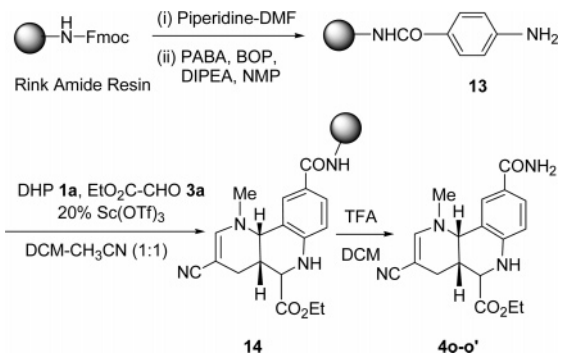
Starting from Merrifield resin, the polymer-supported glyoxylate **11** was prepared in two steps using reported protocols.[37] Treatment with the DHP **1a**, the aniline **2a**, and $Sc(OTf)_3$ as a Lewis Acid in a mixture of $CH_3CN-CH_2Cl_2$ gave the corresponding cycloadduct, which was then cleaved from the resin. This operation allowed the introduction of an additional diversity element (Scheme 6). Thus, when the resin **12** was treated with NaOEt in THF−EtOH, the corresponding sodium carboxylate **4ab**−**ab′** was obtained (85%, 2:1). The HPLC/MS profile of the sample secured the structure and the purity of the compounds thus obtained. The hydrolytic outcome is most likely the result of adventitious water from the resin. However, convenient transesterification protocols were achieved with different alcohols (MeOH and EtOH) under KCN catalysis, and the corresponding esters **4ac**−**ac′** (32%) and **4a**−**a′** (25%, non optimized) were obtained, respectively. Finally, the cleavage of the product from the resin was also performed with $EtNH_2$ in THF−H_2O, providing the corresponding carboxamide **4ad**−**ad′** (30%).[38]

Scheme 6. Solid-Supported MCRs Using Anchored Glyoxylate

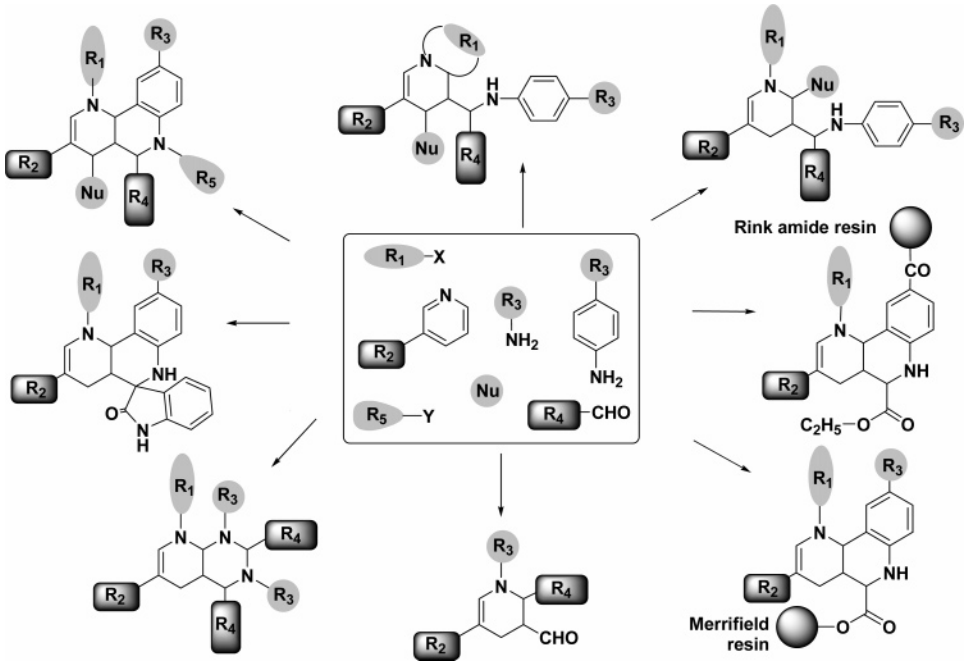


To test the attachment of the aniline component to a solid-support, 4-aminobenzoic acid (PABA) was chosen as a representative aniline and linked to a Rink amide resin. The interaction of the PABA-loaded resin with DHP **1a**, ethyl glyoxylate (**3a**), and $Sc(OTf)_3$ in a mixture of $CH_3CN-CH_2Cl_2$ afforded the corresponding cycloadduct, which was cleaved from the resin with TFA to yield the corresponding products (**4o**−**o′**, 45%), thus illustrating the utility of the procedure (Scheme 7).

Scheme 7. Solid-Supported MCR Using Anchored Aniline



Scheme 8. Diversity of Scaffolds Prepared Using DHPs in MCRs[a]



[a] Scheme drawn for a two-column format.

Conclusion

A simple one-pot procedure was developed to promote the multicomponent aza-Diels−Alder reaction of DHPs, anilines, and carbonyl derivatives without significant interference of the biomimetic reductive pathway. This expands the synthetic use of DHPs, allowing the formation of final products in which the pyridine-derived unit is fused to a tetrahydroquinoline moiety. A careful rational screening was carried out to tune all of the steps of the process. The systematic variation of every component led to a remarkable level of structural diversity, allowing the synthesis of a wide set of attractive scaffolds with great variability. Furthermore, due to the mechanistic particularities of this MCR, interesting skeletal modifications have been described. The modular character of this approach, the simplicity and availability of the majority of building blocks used, and the possibility to perform some of these processes in solid-supported versions, should allow the HTOS of large collections of compounds and its use in DOS processes (Scheme 8).[39]

Experimental Section

General Procedure for the Three-Component Reaction of Dihydroazines with Aldehydes and Anilines. The Lewis acid (0.2 mmol) was added to a solution of aldehyde **3** (1 mmol) and aniline **2** (1 mmol) in dry CH_3CN (4 mL), and the mixture was stirred at room temperature. A solution of dihydropyridine **1** (1 mmol) in dry CH_3CN (3 mL) was then added, and the resulting suspension was stirred at room temperature (unless otherwise specified) under N_2 atmosphere for 12 h. A saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes−EtOAc) to give the desired product.

Parallel Screening of Catalysts, Reaction Conditions and Substrates. Up to 12 simultaneous reactions were run in a Radleys platform, following the general procedure, and were extracted and analyzed with HPLC/MS (H_2O−CH_3CN−1% formic acid; gradient from 100% H_2O to 100% CH_3CN in 20 min; flow 1 mL/min; UV detection at 254 nm; MS-ES$^+$). The presence of the compounds of the chemsets was confirmed upon observation of the expected molecular mass, the ^{1}H NMR diagnostic signals, or both; in most cases, they were purified (flash chromatography) and characterized. The H_2O reaction was run in a water (5 mL)−SDS (0.6 mmol) micellar system; the reagents and the catalyst were added, and the reaction was run for 12 h at room temperature. The high-pressure experiment was performed using the same reagents, catalyst, and solvent ratios at 12 kbar, for 12 h. The microwave-promoted reactions were performed using a focused apparatus with irradiation powers of 25 and 100 W, for 25 and 5 min respectively. The reaction using Yb(III) polystyrylsulfonate (0.75 mmol/g resin loading) was performed keeping the same 20% catalyst ratio in THF−CH_3CN (10 mL, 1:1), and after the filtration, the resin was subjected to a new run under the same conditions.

Solid-Phase Synthesis Using Immobilized Glyoxylate. A suspension of the DHP **1a** (1 equiv, 1.1 mmol, 132 mg), the aniline **2a** (1 equiv, 1.1 mmol, 118 mg), and $Sc(OTf)_3$ (0.2 equiv, 0.22 mmol, 108 mg) in a CH_2Cl_2−CH_3CN mixture (1:1, 10 mL) was added to the glyoxylate-bound resin **11** (prepared in two steps from Merrifield resin [1 g, 1.1 mmol/g]),[36a] and the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered, and the resulting polymer was washed with DMF, THF, and CH_2Cl_2 (10 mL, ×5) and dried in vacuo to give polymer **12**.

Cleavages: (i) Resin **12** (1.3 g) was treated with EtONa (2 equiv, 2.2 mmol, 150 mg) in EtOH−THF (1:1, 10 mL),

and the mixture was stirred for 1 h at room temperature. The mixture was filtered, and the resin was washed with H_2O (10 mL, ×5); the filtrate and washings were evaporated under reduced pressure to give the corresponding sodium carboxylate **4ab**−**ab′** (285 mg, 85% yield). (ii) Resin **12** (1 g) was treated with KCN (14 mg, 0.22 mmol) in MeOH−THF (1:1, 10 mL) or in EtOH−THF (1:1, 10 mL) at 60 °C for 16 h. The mixture was filtered, and the resin was washed with THF (10 mL, ×5). The filtrate and the washings were evaporated to dryness under reduced pressure, and the residue was suspended in H_2O and extracted with EtOAc. The organic layer was dried, filtered, and evaporated to yield the methyl esters **4ac**−**ac′** (105 mg, 32%) and ethyl esters **4a**−**a′** (86 mg, 25%). (iii) The product **4ad**−**ad′** was cleaved from the resin **12** (1 g) by shaking it with a mixture of ethylamine (70% in H_2O, 5 mL) and THF (5 mL) at room temperature for 16 h. The mixture was filtered, and the resin was washed with MeOH−THF (1:1, 10 mL, ×3 times). The filtrate and washings were concentrated to provide the amide **4ad**−**ad′** (103 mg, 30%)[38a] as the usual 2:1 mixture of stereoisomers.

Solid-Phase Synthesis Using Immobilized Aniline. Rink amide resin (1 g, 0.57 mmol/g) was treated with a solution of piperidine (1 mL) in DMF (4 mL) (×3) then filtered and washed with DMF and CH_2Cl_2 (5 mL, ×5). The resin was then mixed with BOP (2 equiv, 1.14 mmol, 442 mg), DIPEA (2 equiv, 1.14 mmol, 0.2 mL), and PABA (1 equiv, 0.57 mmol, 78 mg) in 5 mL of NMP, and the mixture was stirred at room temperature overnight. The resin vas filtered and washed with NMP, DMF, and CH_2Cl_2 (5 mL, ×5). A suspension of the DHP **1a** (1 equiv, 0.57 mmol, 68 mg), ethyl glyoxylate **3a** (1 equiv, 0.57 mmol, 110 μL) and $Sc(OTf)_3$ (0.2 equiv, 0.11 mmol, 54 mg) in a CH_2Cl_2−CH_3-CN mixture (1:1, 5 mL) was added to the PABA-loaded resin **13**. The mixture was shaken at room temperature overnight, then filtered and washed with DMF, THF, and CH_2Cl_2 (5 mL, ×5). The dried resin **14** (1 g) was treated with 5 mL of 10% TFA in CH_2Cl_2 for 30 min, then filtered and washed with CH_2Cl_2. The filtrates were evaporated under reduced pressure to give the product **4o**−**o′** (117 mg, 45% yield). Treatment with aqueous Na_2CO_3 and extraction with CH_2-Cl_2 afforded the free base, which was positively identified with an independent sample of **4o**−**o′** obtained in the solution-phase experiment.

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Supporting Information Available. Characterization data for synthetic compounds. This material is available free of charge via the Internet at htpp://pubs.acs.org.

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