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New Light on an Old Story: Facile and Efficient Synthesis of 1,3-Diaryl-5-spirohexahydropyrimidines via a Six-Molecule, Three-Component Mannich-Type Reaction

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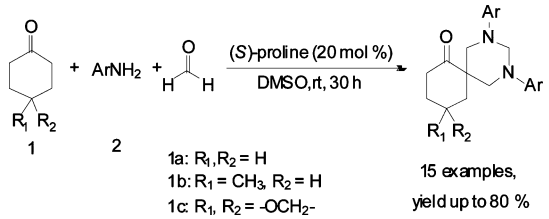

A facile and efficient synthesis of 1,3-diaryl-5-spirohexahydropyrimidines via a one-pot condensation of anilines, formaldehyde, and cyclohexanones is reported. In this one-pot, three-component reaction, six molecules of reactants are involved and six new covalent bonds are generated. Bicyclic products are obtained from the starting materials in one pot using readily available starting materials and catalysts.

Various natural products and pharmaceutical agents containing the hexahydropyrimidine moiety exhibit a broad range of biological activities.[1] *N*-Substituted hexahydropyrimidines are synthetic intermediates for spermidine-nitroimidazole drugs for the treatment of A549 lung carcinoma[2] and structural units in new trypanothione reductase inhibiting ligands for the regulation of oxidative stress in parasite cells.[3] Some suitably substituted derivatives have metal-complexing properties. Based on tetrahydropyrimidin-2-ylidenes, Bucheister and co-workers recently synthesized a new class of *N*-heterocyclic carbene complexes of Ag(I), Pd(II), Rh(I), Ir(I), and Ru(IV) and applied them to various C−C and C−Si coupling reactions.[4] Hexahydropyrimidines are prepared classically by condensation of substituted propane-1,3-diamines with aldehydes and ketones.[4a,b,5,6] In organic synthesis, the hexahydropyrimidine nucleus has been employed as a protecting group in selective acylations and additions of 1,3-diamines due to its easy cleavage in mild acidic medium.[6]

Inspired by the initial investigation of the proline-catalyzed enantioselective α-aminomethylation of ketones developed by Córdova[7n,x] and Bolm[8] and the classical method for synthesis of hexahydropyrimidines, we attempted to develop a facile and efficient access to 1,3-diaryl-5-spirohexahydropyrimidines via a one-pot condensation of anilines, formaldehyde, and cyclohexanones. The reactants of the one-pot, three-component reaction have been involved in the classical Mannich reaction, which was discovered in 1912[9] and is one of the most important C−C bond-forming reactions for production of nitrogenous molecules,[10] such as amino acids and amino alcohols. Since List reported the first one-pot, three-component Mannich reaction between in situ generated imines and unmodified ketones as donors,[11] interest in amino acids and their derivatives-catalyzed asymmetric variants of the Mannich reaction has

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grown considerably.[7] Moreover, excellent asymmetric Mannich-type reactions catalyzed by organocatalysts have been reported.[12]

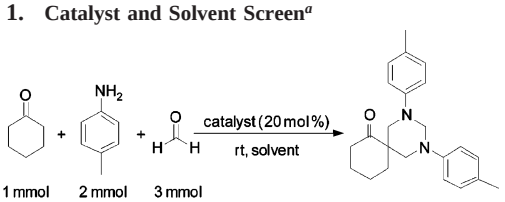
The efficiency of multicomponent reactions can be judged by the number of bonds formed and the increase in molecular complexity. The protocol we designed to synthesize 1,3-diaryl-5-spirohexahydropyrimidines is efficient since six molecules are involved in the reaction and six new covalent bonds are generated. To the best of our knowledge, synthesis of spiro compounds via sequential introduction of two aminomethyls on the same α-carbon of carbonyl is unprecedented.

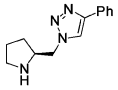
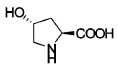
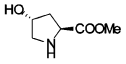
To begin this study, we chose cyclohexanone, aqueous formaldehyde, and 4-methylaniline as the standard substrates to search for potential catalysts and suitable reaction conditions. We investigated several cyclic secondary amines' ability to mediate the model reaction (Table 1). All of the catalysts investigated could catalyze the reaction and furnished the desired products in low to moderate yields. Among them, (*S*)-proline catalyzed the reaction with the highest yield under the set reaction conditions. Then, we examined several solvents with (*S*)-proline as catalyst and the highest efficiency was obtained in DMSO.

In attempts to improve the yield, we adjusted the ratio of the reactants, and the processes are shown in Table 2. The reaction proceeded in DMSO with (*S*)-proline as catalyst. The amount of cyclohexanone was fixed to 1 mmol. When the amounts of 4-methylaniline and formaldehyde were increased, the yield of the desired product increased until the ratio of cyclohexanone, 4-methylaniline, and formaldehyde was up to 1:3:6 (entry 6). Further increase in the amounts of 4-methylaniline and formaldehyde resulted in a slight decrease in yield (entries 9 and 10). Furthermore, the reaction temperature was also investigated. However, when the temperature was increased to 40 or 60 °C, a lower yield was obtained (entries 7 and 8).

Thus, under the optimized conditions, various anilines and cyclohexanones were reacted with aqueous formaldehyde smoothly, and the corresponding results are listed in Table 3. In general, the substrates employed could obtain presentable results. On the whole, the better yields were obtained with cyclohexanone. Cyclohexanone showed better reactivity than 4-methylcyclohexanone and lightly higher yields were obtained. However, 1,4-dioxaspiro[4.5]decan-8-one is much less active than cyclohexanone (compare entries 1−4 and 12−15). The anilines with electron-withdrawing groups behave low actively in the reaction, and only medium yields were obtained (entries 4, 7, and 15). The main limitation of the six molecules participated three-component reaction has been the requirement to use anilines as the amine component and cyclohexanones as the cyclic ketone component. The X-ray analysis of product **n**

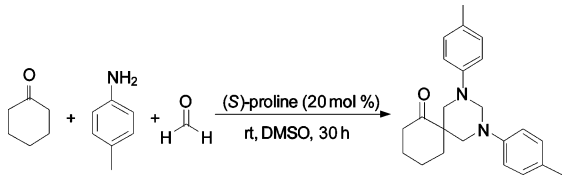
TABLE 1. Catalyst and Solvent Screen[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1		DMSO	25
2		DMSO	5
3		DMSO	28
4		DMSO	38
5		DMSO	30
6		DMSO	6
7	**(*S*)-proline**	**DMSO**	**42**
8	(*S*)-proline	NMP	3
9	(*S*)-proline	THF	38
10	(*S*)-proline	DMF	33
11	(*S*)-proline	MeOH	39
12	(*S*)-proline	CH_3CN	29

[a] Experimental conditions: a mixture of cyclohexanone (1 mmol, 1 equiv), 4-methylaniline (2 mmol, 2 equiv), formaldehyde (3 mmol, 3 equiv, 36% aqueous solution), and organocatalyst (20 mol %) in 4 mL of solvent was stirred at room temperature for 30 h. The crude product obtained after aqueous workup was purified by column chromatography. [b] Isolated yields.

TABLE 2. Equivalent Screen[a]



entry	cyclohexanone (mmol)	4-methylaniline (mmol)	formaldehyde (mmol)	yield[b] (%)
1	1	2	3	42
2	1	2	3.2	43
3	1	2.3	3.3	47
4	1	2.5	3.6	52
5	1	3	4.5	63
6	**1**	**3**	**6**	**73**
7	1	3	6	47[c]
8	1	3	6	40[d]
9	1	3	6.5	65
10	1	3.5	7	67

[a] Experimental conditions: a mixture of cyclohexanone, 4-methylaniline, formaldehyde (36% aqueous solution), and organocatalyst (20 mol %) in 4 mL of DMSO was stirred at room temperature for 30 h. The crude product obtained after aqueous workup was purified by column chromatography. [b] Isolated yields. [c] At 40 °C. [d] At 60 °C.

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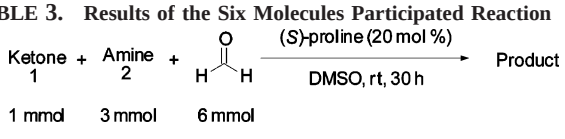
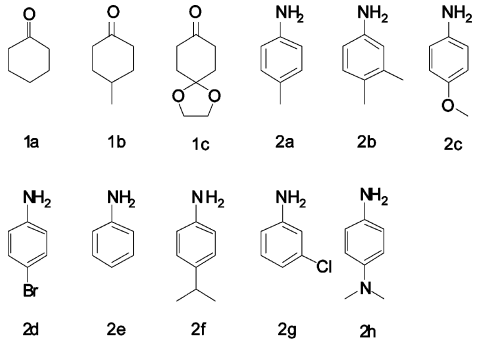
TABLE 3. Results of the Six Molecules Participated Reaction



entry	ketone	amine	product	yield[a] (%)
1	**1a**	**2a**	**a**	73
2	**1a**	**2b**	**b**	74
3	**1a**	**2c**	**c**	80
4	**1a**	**2d**	**d**	48
5	**1a**	**2e**	**e**	53
6	**1a**	**2f**	**f**	75
7	**1a**	**2g**	**g**	45
8	**1a**	**2h**	**h**	67
9	**1b**	**2a**	**i**	71
10	**1b**	**2b**	**j**	72
11	**1b**	**2c**	**k**	74
12	**1c**	**2a**	**l**	48
13	**1c**	**2b**	**m**	43
14	**1c**	**2c**	**n**	65
15	**1c**	**2d**	**o**	33

[a] Isolated yields.



was performed to confirm that the molecular structure is indeed as shown in Figure 1.

A tentative mechanism for the reaction is proposed in Scheme 1. The ketone undergoes twice α-aminomethylation reactions in succession on the same α-carbon of carbonyl-catalyzed by proline. The condensation of the resulting substituted propane-1,3-diamine with formaldehyde furnishes the desired spirohexahydropyrimidine. Using Mannich bases instead of cyclohexanones as reactants can also generate the desired products.

In conclusion, we have developed a simple and efficient method for the preparation of 1,3-diaryl-5-spirohexahydropyrimidines via proline-catalyzed one-pot condensation of anilines, aqueous formaldehyde, and cyclohexanones. In this one-pot, three-component reaction, six molecules of reactants are involved and six covalent bonds are generated.

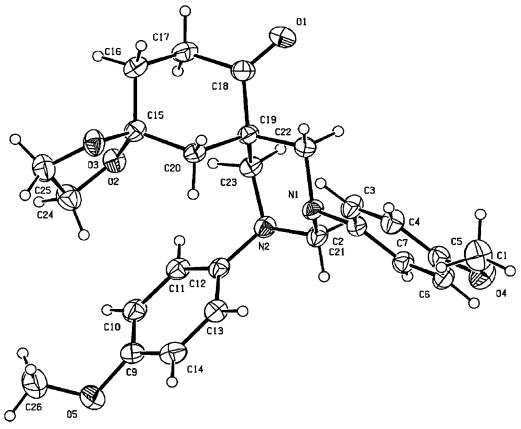
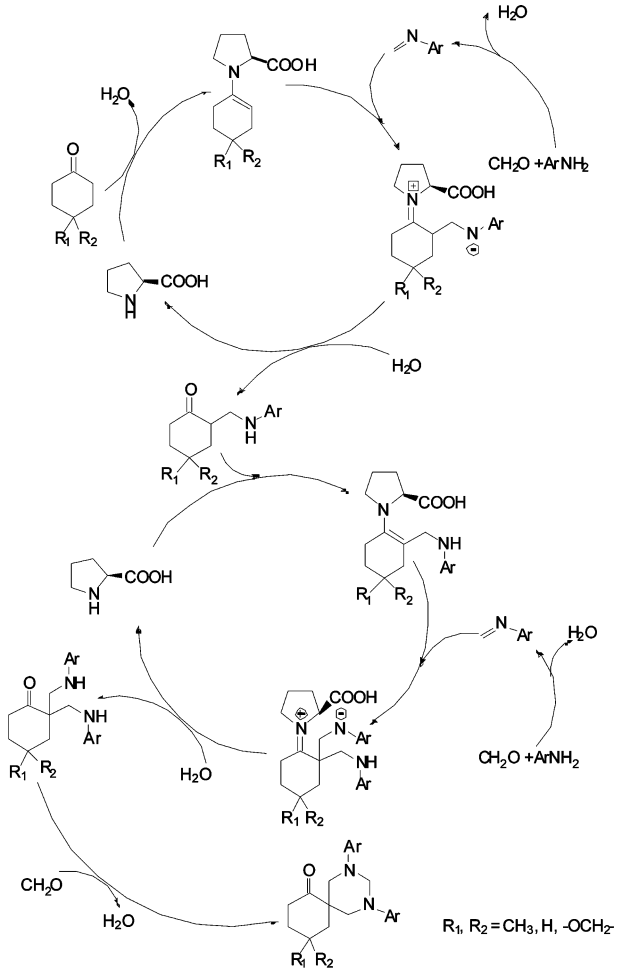


FIGURE 1. Molecular structure for the product **n** as determined by X-ray analysis.

SCHEME 1. Proposed Mechanism for the Reaction



Experimental Section

General Procedure for the Six-Molecule, Three-Component Reaction. A mixture of ketone (1 mmol), aniline (3 mmol), formaldehyde (6 mmol, 36% aqueous solution), and a catalytic amount of (*S*)-proline (20 mol %) in 4 mL of DMSO was stirred at room temperature. After 30 h, the reaction was quenched by addition of aqueous $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried with Na_2SO_4, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure, and the crude product mixture was purified by silica gel column chromatography (EtOAc/petroleum ether, a little Et_3N).

Product a: 2,4-di-*p*-tolyl-2,4-diazaspiro[5.5]undecan-7-one: white solid; mp 124−125 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm) 7.08 (d, J = 8.4 Hz, 4H), 6.44 (d, J = 8.4 Hz, 4H), 4.78 (d, J = 11.4 Hz, 1H), 4.08 (d, J = 11.4 Hz, 1H), 3.51 (d, J = 12.6 Hz, 2H), 3.38 (d, J = 12.6 Hz, 2H), 2.37 (t, J = 6.9 Hz, 2H), 2.27 (s, 6H), 1.89−1.81 (m, 4H), 1.66−1.65 (m, 2H); ^{13}C NMR and DEPT (75 MHz, $CDCl_3$) δ (ppm) 213.2 (C═O), 147.8 (C), 129.7 (CH), 117.4. (CH), 69.4 (CH_2), 55.4 (CH_2), 50.0 (C), 39.2 (CH_2), 34.6

(CH_2), 27.7 (CH_2), 20.9 (CH_2), 20.5 (CH_3); IR (KBr) 2928, 1703, 1514, 1452, 1234, 1210, 811 cm^{-1}. Anal. Calcd (found) for $C_{23}H_{28}N_2O$: C, 79.27 (79.20); H, 8.10 (7.92); N, 8.04 (8.11).

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Supporting Information Available: Crystallographic data for product **n** (CIF), copies of ^1H and ^{13}C NMR spectra, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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