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A Convenient Alternative Route to β-Aminoketones

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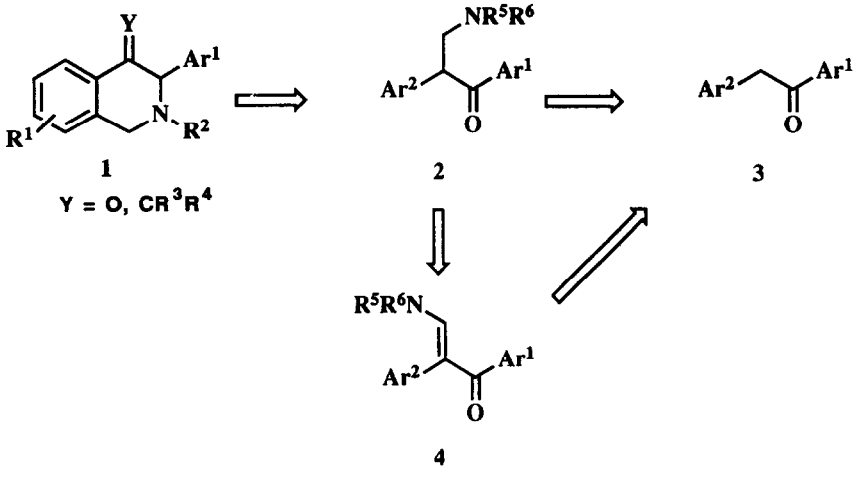
Abstract: Enaminones has been prepared and submitted to conjugate reduction with LAH and the system Al_2O_3/R_2NH to give β-aminoketones. The latter tandem amination system has also been applied in the Mannich reaction, improving the synthesis of several new diaryl β-aminoketones. Besides, the sequential use of DMFDMA and LAH-CuI on deoxybenzoins furnishes a new route for the synthesis of enones.

Regarding our investigations on 3-arylisoquinoline alkaloids[1] we were interested in developing a new synthetic route to C-4 functionalized 3-arylisoquinoline derivatives **1** through β-aminoketone intermediates **2**.



1 Y = O, CR^3R^4 **2** **3** **4**

The diaryl β-aminoketones **2** can be made mainly by two ways: applying the Mannich reaction to deoxybenzoins **3** and by conjugate reduction of enaminones **4**. However, under Mannich conditions deamination and deaminomethylation are very common side reactions, specially with diaryl derivatives like **2**.[2]

On the other hand, in our opinion, the conjugate reduction of enaminone derivatives using the Adams catalyzed hydrogenation[3] or a complex hydride like LAH[4] should be revised as to date, different synthetic results have been proposed.[2,5,4b-e] Furthermore, the reagents usually applied to the selective conjugate reduction of enones[6] have never been used on enaminones.

These facts prompted us to attempt a convenient alternative preparation of enaminones **4** and β-aminoketones **2** and we report here the results obtained when adequate deoxybenzoins were used as starting material.

Results and Discussion

A. Synthesis and reduction of enaminones.

Following the Abdulla's method,[4f] we made enaminoketone derivatives **4** by reaction of commercial ketones **3a-c** with *N,N*-dimethylformamide dimethyl acetal (DMFDMA). Afterwards, we modified the already mentioned procedure thus obtaining better yields for diaryl enaminones **4d** and **4e**.[7](Table 1).

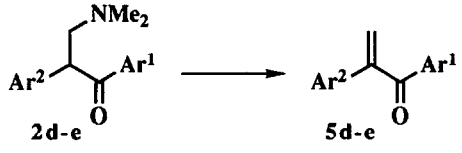
3 **4**

Table 1. Synthesis of enaminoketones **4**.

Product	R^1	R^2	Yield[a](%)
4a	$-(CH_2)_4-$		66[b]
4b	Ph	H	80[b]
4c	p-MeOPh	H	70[b]
4d	Ph	Ph	89
4e	3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	95

[a]Yield of pure crystallized compound
[b]Made according to reference 4f

With enaminoketones **4** in hand, we undertook the corresponding reduction and we obtained the following synthetic results. Since the LAH-CuI system has shown selectivity in the conjugate reduction of different enones,[6h-j] we applied the latter conditions to enaminones **4b-e** thus obtaining C=C bond reduction products, but in the reaction medium the so-formed β-aminoketones **2b-e** were very unstable giving rise to the formation of enone derivatives. This behaviour was specially observed in the case of **2d** and **2e**, which suffered deamination reaction to afford the corresponding diarylpropenones **5d** and **5e** quantitatively.



Consequently, we tried the catalytic hydrogenation over Pd-C[4b,5a] for the same purpose but in some cases we recovered unreacted material (**4b** and **4c**) and in other cases (**4d** and **4e**), we detected formation of hydrogenolysis products like starting deoxybenzoin and α-methylketone derivatives.

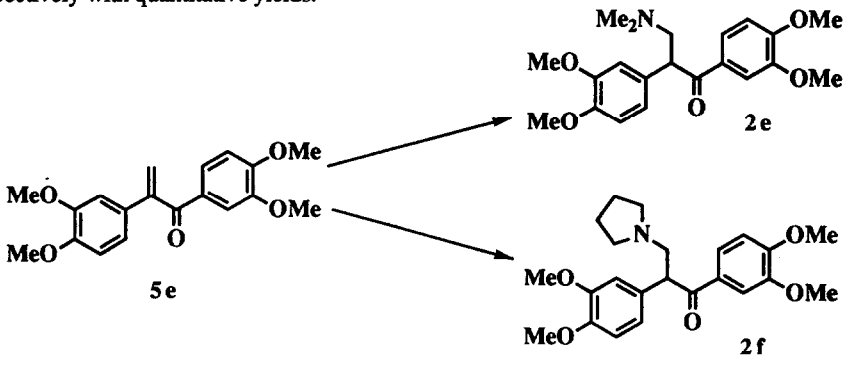
Finally, the use of the complex hydride LAH and hydrogenation over the Adams catalyst (PtO_2)[3] were explored and the obtained results along with those of the LAH-CuI system are shown in Table 2.

Table 2. Attempts for conjugate reduction of enaminones **4**.

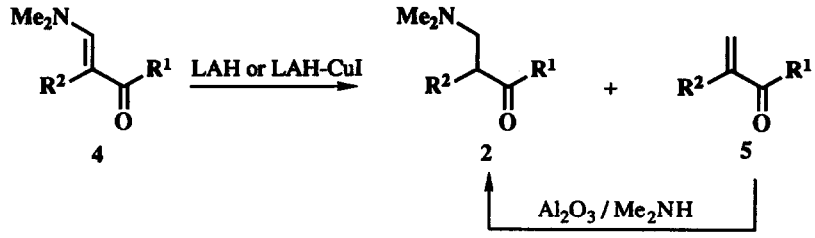
Reduction system	Enaminone **4**	ß-Aminoketone **2**(%)	Side-products(%)
H_2/PtO_2	4b	2b (70)	---
	4c	2d (60)	---
	4d	---	Hydrogenolysis(42)
	4e	---	Hydrogenolysis(27)
LAH-CuI	4b	2b (50)	5b (10)
	4c	2c (40)	5c (5)
	4d	---	5d (98)
	4e	---	5e (98)
LAH	4b	2b (60)	5b (9)
	4c	2c (65)	5c (4)
	4d	2d (55)	5d (43)
	4e	2e (35)	5e (55)

From our results, we may propose that the best way to make β-aminoketones implies the use of LAH. Nevertheless, the yields of **2d** an **2e** were still low and formation of a significative amount of deamination products was detected. Besides, as we had previously observed, the former compounds were very unstable in solution, affording diarylpropenones **5d** and **5e**. Therefore, we had still the need of a method good enough to reduce enaminones to β-aminoketones.

Taking into account that Al_2O_3 (Activity III) had already been used as a catalyst in the Michael type addition of secondary amines to α,β-unsaturated ketones,[8] we explored the addition of dimethylamine and pyrrolidine to diarylpropenone **5e** under the already mentioned conditions, thus obtaining the expected β-aminoketones **2e** and **2f** respectively with quantitative yields.



With these results in hand, we carried out the hydride conjugate reduction of several enaminones **4** using alumina as catalyst and we observed that the yields of β-aminoketones from enaminones were largely improved.



On the other side, it should be pointed out that in spite of the failure of the LAH-CuI system to afford regioselectively the target β-aminoketone, nevertheless this system implies a valid alternative to make α,β-unsaturated ketones **5** starting from the corresponding carbonyl compounds showing considerable advantage over other procedures described in the literature (Table 3).

Table 3. Preparation of α,β-unsaturated ketones **5**.

Enone **5**		Method	Yield (%)	Reference
R^1	R^2			
CH_3	Ph	Mannich/Hoffmann	60	2
Ph	Ph	Mannich	70	7a
Ph	Ph	DMFDMA/LAH/Hoffmann	80	4g
Ph	Ph	TAMA[a]	95	9
Ph	Ph	DMFDMA/LAH-CuI	89	This paper
3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	DMFDMA/LAH-CuI	95	This paper

[a] TAMA: N-methylanilinium trifluoroacetate.

B. Direct synthesis of β-aminoketones.

When we applied the Mannich conditions to several diarylketones we observed the formation of the expected β-aminoketones but in very low yields, probably due to typical side reactions like deaminomethylation and deamination.[2] Besides, the already mentioned undesired transformations became more important as the substitution on the aromatic rings increased.

However, addition of Al_2O_3 to the reaction mixture furnished β-aminoketones **2d-j** with fair to good yields (Table 4), thus providing a good method to make the objective compounds **2** directly from the corresponding deoxybenzoins **3**.

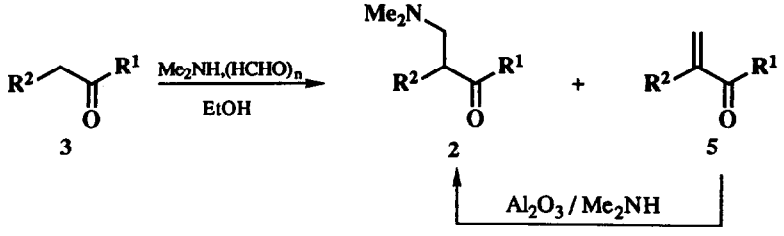
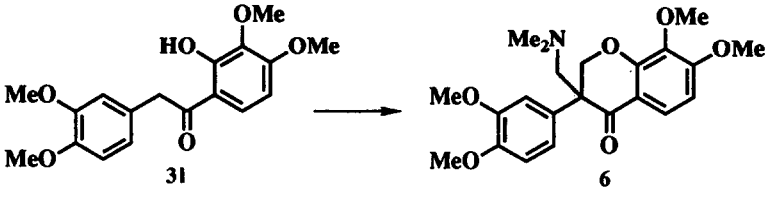


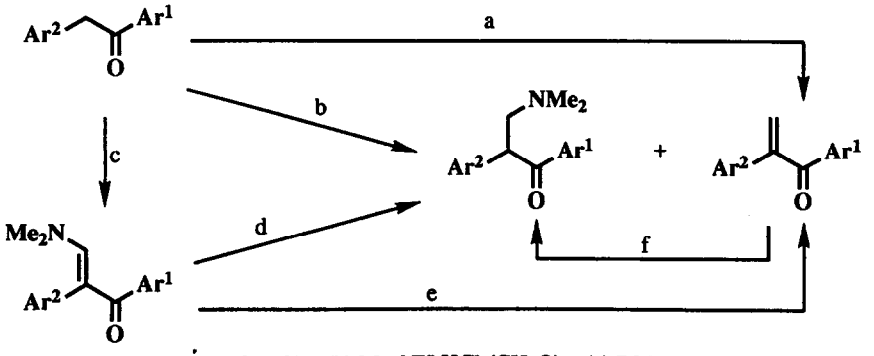
Table 4. Synthesis of β-aminoketones **2**.

	β-Aminoketones **2**		Yield (%)
	R^1	R^2	
2d	Ph	Ph	87
2e	3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	70
2g	3,4-$(MeO)_2$Ph	4-Bn-3-MeOPh	60
2h	3,4-$(MeO)_2$Ph	2-Br-4,5-$(MeO)_2$Ph	25
2i	3,4-$(MeO)_2$Ph	3,4,5-$(MeO)_3$Ph	60
2j	2,3-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	61
2k	2,3,4-$(MeO)_2$Ph	3,4-$(MeO)_2$Ph	65

Only in the case of phenolic ketone **3l** we observed a special behaviour, since we obtained the isoflavanone **6** as the major product (92%). A similar result had been previously reported by our group[7a] when applying the classical Mannich conditions to derivative **3l**, although a smaller amount of **6** was then isolated (21%).



To sum up, synthetic yields of enaminones from deoxybenzoins and DMFDMA have been improved by changing experimental conditions. Besides, β-aminoketone synthesis by conjugate reduction of enaminones has been efficiently carried out by using LAH or LAH-CuI along with Al_2O_3. On the other hand, due to the fact that the former derivatives can be conveniently prepared submitting the corresponding deoxybenzoins to Mannich reaction conditions using Al_2O_3 as a catalyst, unwanted side reactions like retro-Mannich or deamination processes are avoided. Finally, the sequential use of DMFDMA and LAH-CuI on 1,2-diarylketones constitutes an advantageous route for the preparation of α,β-unsaturated ketones.



Reagents: (a) $Me_2NH,(CH_2O)_n$;(b) Me_2NH-HCl,$(CH_2O)_n$;(c) DMFDMA ;(d) LAH ; (e) LAH-CuI ; (f) Me_2NH,Al_2O_3.

Experimental

Solvents were either purified according to methods described by Perryn *et al.*,[10] or used as received from the manufacturers, depending on their purity. Neutral alumina Merck (70-230 mesh ASTM) was used. Thin layer chromatography (tlc) was performed on plates coated to a thickness of 0.2 mm with Merck Kieselgel 60 F_{254} using UV light (254 nm) and Dragendorff's reagent[11] as developing agents. Evaporation of solvents under reduced pressure was performed in a Heidolph VV 60 rotatory evaporator. Melting points were measured in a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer R-1430 infrared spectrophotometer as KBr plates, as neat liquid or in $CHCl_3$ and peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker ACE-250 (250 MHz for ^1H and 62.83 MHz for ^{13}C). Chemical shifts (δ) were measured in ppm relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26 for ^1H or 77.00 for ^{13}C) as internal standards.Multiplicities are indicated by s (singlet), b s (broad singlet) d (doublet), t (triplet), m (multiplet), or dd (doublet of doublets). Coupling constants, J, are reported in hertz. ^{13}C DEPT experiments were used to assist with the assignation of the signals.Mass spectrum (EI) was obtained on a MS902 model Kratos apparatus. Data are reported in the form m/z (intensity relative to base =100). Combustion analyses were performed on a Perkin-Elmer 2400 CHN apparatus.

Synthesis of enaminoketones.

2-[(Dimethylamino)methylen]cyclohexanone **4a**. Typical procedure. This was prepared using the method of Abdulla[4f]. DMFDMA (7.7 ml, 0.05 mol) was added dropwise to neat cyclohexanone **3a** (5 g, 0.05 mol) under nitrogen at room temperature and the mixture was refluxed under nitrogen for 12 h. After cooling, methanol was removed *in vacuo* and the residue distilled in a Kugelrohr apparatus to afford the enaminone **4a** (5.1 g, 66%) as an amber oil (130°C/0.3 mmHg), (Lit.[4f] 90°C/0.03 mmHg), R_f(hexane-EtOAc, 1:1) 0.3, ν_{max} 1660 (C=O); δ_H 1.60-1.70 (4H, m, H-5 and H-4), 2.29 (2H, t, *J* 6.2, H-6 or H-3), 2.64 (2H, t, *J* 6.2, H-3 or H-6), 3.04 (6H, s, NMe_2) and 7.46 (1H, s, =CH-N)(Found: C, 70.65; H, 9.6; N, 9.3. $C_9H_{15}ON$ requires C, 70.55; H, 9.85; N, 9.15%).

3-(N,N-Dimethylamino)-1-phenyl-2-propen-1-one **4b**. This was prepared as above using DMFDMA (11 ml, 0.1 mol) acetophenone **3b** (10 g, 0.08 mol) and dry toluene (100 ml). After removing the solvent the residue crystallized from diethyl ether to give the enaminone **4b** (11.8 g, 80%) as needles, m.p. 87-90°C(diethyl ether)(Lit.[12] 90°C(ethanol)), R_f(hexane-EtOAc, 1:1) 0.1, ν_{max} 1650 (C=O); δ_H 2.93 (3H, b s, NMe), 3.07 (3H, b s, NMe), 5.69 (1H, d, *J* 12.4, *CH*-CO), 7.34-7.46 (3H, m, H-3_{arom}, H-4_{arom} and H-5_{arom}), 7.74 (1H, d, *J* 12.4, =CH-N) and 7.87 (2H, dd, *J* 7.5 and *J* 1.9, H-2_{arom}, H-6_{arom},); δ_C 37.1 (NMe), 44.9 (NMe), 92.1 (*C*H-CO), 127.3, 128.0, 130.7 (C_{arom}-H), 140.5 (C_{arom}-C), 155.1 (=CH-N) and 188.5 (CO)(Found: C, 75.25; H, 7.6; N, 8.3. $C_{11}H_{13}ON$ requires C, 75.4; H, 7.5; N, 8.0%).

3-(N,N-Dimethylamino)-1-(4-methoxyphenyl)-2-propen-1-one **4c** This was prepared as above using DMFDMA (0.7 ml, 6.2 mol), commercial ketone **3c** (1.1 g, 5 mol) and dry toluene (25 ml). 0.77 g of enaminone **4c**.70% were obtained as a yellow solid, m.p. 94-96°C(diethyl ether)(Lit.[13] 92-93°C(ethanol)), R_f(hexane-EtOAc, 1:1) 0.1; δ_C 37.4 (NMe), 45.0 (NMe), 55.2 (MeO) 91.6 (*C*H-CO), 113.2, 129.3, (C_{arom}-H), 133.0 (C_{arom}-C), 155.0 (=CH-N), 161.8 (C_{arom}-O) and 187.3 (CO)(Found: C, 70.45; H, 7.6; N, 6.6. $C_{12}H_{15}O_2N$ requires C, 70.2; H, 7.35; N, 6.8%).

1,2-Diphenyl-3-(N,N-dimethylamino)-2-propen-1-one **4d**. DMFDMA (4 ml, 0.03 mol) was added dropwise to a stirred solution of commercial benzyl phenyl ketone **3d** (5 g, 0.025 mol) in dry toluene under nitrogen at room temperature. After 12 h DMFDMA (0.1 ml, 0.8 mmol) was added and the mixture heated to 50°C for another 24 h. Then, during five days DMFDMA (0.1 ml, 0,8 mmol) was added and the heating temperature increased about 15°C everyday. The fifth day, as the reaction finished (tlc monitoring), the solvent was removed *in vacuo*, and the residue was crystallized from diethyl ether to afford the enaminoketone **4d** (5,6 g, 89%) as a yellow solid, m.p. 124-126°C(diethyl ether)(Lit.[7] 124-126°C(methanol)), R_f(hexane-EtOAc, 1:1) 0.1; ν_{max} 1635 (C=O); δ_H 2.75 (6H, s, NMe), 7.14-7.28 (8H, m, H_{arom}), 7.34 (1H, s, =CH-N) and 7.42 (2H, dd, *J* 6.1, *J* 1.6, H-2_{arom}, H-6_{arom})(Found: C, 81.05; H, 7.0; N, 5.6. $C_{17}H_{17}ON$ requires C, 81.25; H, 6.8; N, 5.55%).

3-(N,N-Dimethylamino)-1,2-bis-(3,4-dimethoxyphenyl-2-propen-1-one **4e**. This was prepared as above using DMFDMA (4.3 ml, 32 mol) ketone **3e**[14] (11 g, 0.03 mol) and dry toluene (25 ml), 10 g of enaminone **4e** (90%) were obtained as a yellow powder, m.p. 153-154°C(diethyl ether); (Lit.[7a] 153-154°C(methanol)),

R_f(hexane-EtOAc, 1:1) 0.1; ν_{max} 1635 (C=O); δ_H 2.77 (6H, s, NMe), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 3.89 (6H, s, OMe), 6.68-6.80 (4H, m, H-2"arom, H-5"arom, H-5'arom, H-6"arom), 7.05-7.10 (2H, m, H-2'arom, H-6'arom) and 7.41 (1H, s, =CH-N); δ_C 43.1 (NMe), 55.5 (MeO), 109.4, 110.3 (C_{arom}-H), 111.0 (=*C*-CO), 112.1, 115.1, 122.3, 124.2 (C_{arom}-H), 130.1, 133.9 (C_{arom}-C), 152.8 (=CH-N), 193.3 (CO)(Found: C, 68.05; H, 7.0; N, 3.6. $C_{21}H_{25}O_5N$ requires C, 67.9; H, 6.8; N, 3.75%).

Catalytic conjugate reduction with the Adams catalyst.

1-*Phenyl*-3-*(N,N-dimethylamino)propan*-1-*one* **2b**. Typical procedure. A mixture of enaminoketone **4b** (1 g, 5.7 mmol) and prereduced Adams catalyst (from 0.03 g of platinum oxide) in 20 ml of glacial acetic acid was hydrogenated for 4 hours (P_{H2}=3atm). The mixture was filtered, the filtrate basified with a sodium hydroxide solution and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and evaporated to afford β-aminoketone **2b** (0.7 g, 70%) as a colourless oil, (Lit.[15] 31-33°C(ethanol)), R_f(CH_2Cl_2-EtOAc, 9:1) 0.15; ν_{max} 1690 (C=O); δ_H 2.29 (6H, s, NMe), 2.77 (2H, t, *J* 7.3, CH_2-N), 3.16 (2H, t, *J* 7.3, CH_2-CO), 7.40-7.59 (3H, m, H-3arom, H-4arom and H-5arom) and 7.94-7.98 (2H, m, H-2arom, H-6arom); δ_C 30.3 (CH_2-N), 45.4 (NMe_2), 54.3 (*C*H_2-CO), 128.0, 128.6, 133.1 (C_{arom}-H), 136.9 (C_{arom}-C) and 199.1 (CO)(Found: C, 74.35; H, 8.7; N, 8.1. $C_{11}H_{15}ON$ requires C, 74.55; H, 8.55; N, 7.9%).

3-*(N,N-Dimethylamino)*-1-(4-*methoxyphenyl)propan*-1-*one* **2c**. This was prepared as above using 0.08 g (0.4 mmol) of enaminoketone **4c**, Adams catalyst (0.005 g) and 10 ml of glacial acetic acid. Hydrogenation (P_{H2}=3atm) for 4 h afforded 0.06 g of ketone **2c** (60%) as a colourless oil, (Lit.[16] 32-33°C(ethanol)), R_f(CH_2Cl_2-EtOAc, 9:1) 0.15; ν_{max} 1690 (C=O); δ_H 2.29 (6H, s, NMe), 2.76 (2H, t, *J* 7.3, CH_2-N), 3.11 (2H, t, *J* 7.3, CH_2-CO), 3.85 (3H, s, MeO), 6.92 (2H, dd, *J* 8.9, *J* 2.1, H-3arom, H-5arom) and 7.93 (2H, dd, *J* 8.9, *J* 2.1, H-2arom, H-6arom)(Found: C, 69.3; H, 8.5; N, 6.9. $C_{12}H_{17}O_2N$ requires C, 69.55; H, 8.25; N, 6.75%).

Conjugate reduction with LAH.

1-*Phenyl*-3-*(N,N-dimethylamino)propan*-1-*one* **2b**. Typical procedure. Solid enaminone **4b** (0.23 g, 1.3 mmol) was added to an ice-cooled stirred suspension of LAH (0.15 g, 4 mmol) in dry THF (50 ml). After stirring overnight, ethyl acetate (7 ml) was added slowly, followed by water (7 ml). The mixture was filtered, and the filtrate evaporated under reduced pressure. The residue was acidified with HCl 1M solution, washed with hexane, the aqueous layer basified to pH 9 with ammonium hydroxide solution and extracted with dichloromethane, dried over anhydrous sodium sulfate and evaporated to afford β-aminoketone **2b** (0.14 g, 60%).

The same procedure on enaminoketone **4c** (0.09 g, 0.44 mmol) gave a 65% of 3-*(N,N-dimethylamino)*-1-(4-*methoxyphenyl)propan*-1-*one* **2c**.

The same procedure on enaminoketone **4d** (1 g, 4 mmol) afforded the following products:

1,2-*Diphenyl*-3-*(N,N-dimethylamino)propan*-1-*one* **2d** (55%), m.p. of hydrochloride 164-165°C (ethanol)(Lit.[17] 165-168°C(ethyl acetate)), R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1690 (C=O); δ_H 2.29 (6H, s, NMe), 2.64 (1H, dd, *J* 12.3, *J* 4.6, CH_aH_b-N), 3.44 (1H, dd, *J* 12.3, *J* 9.0, *C*H_aH_b-N), 4.93 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 7.17-7.55 (8H, m, H_{arom}) and 7.99 (2H, d, *J* 7.3, H-6'arom, H-2'arom); δ_C 46.6 (NMe_2), 51.0 (*C*H-CO), 62.5 (CH_2-N), 127.5, 128.2, 128.3, 1128.6, 129.1 (C_{arom}-H), 132.0 (C_{arom}-C), 133.0 (C_{arom}-H),137.5 (C_{arom}-C) and 198.0 (CO); m/z 254.2 (M^+, 37), 208.1(66), 196.1(69), 178.1(21), 165.1(90)148.1(45), 133.1(38), 118.0(44), 105.0(55), 91.1(30), 77.0(50), 58.1(100), 51.9(29), 42.0(30)(Found: C, 80.3; H, 7.7; N, 5.7. $C_{17}H_{19}ONH$ requires C, 80.3; H, 7.95; N, 5.5%).

1,2-*Diphenyl*-2-*propen*-1-*one* **5d** (43%), m.p. 28-29°C (diethyl ether)(Lit.[18] 28-30°C(ethanol)), R_f(hexane-EtOAc, 1:1) 0.95.

The same procedure applied to enaminoketone **4e** (5 g, 4.1 mmol) afforded the following products:

3-*(N,N-Dimethylamino)*-1,2-*bis*-*(*3,4-*dimethoxyphenyl)propan*-1-*one* **2e** (35%), m.p. of hydrochloride 214-216°C(ethanol), R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1690 (C=O); δ_H 2.26 (6H, s, NMe), 2.53 (1H, dd, *J* 12.3, *J* 4.6, CH_aH_b-N,), 3.32 (1H, dd, *J* 12.3, *J* 9.0, CH_aH_b-N), 3.81 (3H, s, MeO), 3.85 (3H, s, MeO), 3.88 (6H, s, MeO), 4.74 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 6.76-6.89 (4H, m, H_{arom}), 7.53 (1H, d, *J* 1.9, H-2'arom) and 7.65 (1H, dd, *J* 8.4, *J* 1.9, H-6'arom); δ_C 45.9 (NMe_2), 50.9 (*C*H-CO), 55.4, 55.5, 55.6, 55.7 (OMe), 63.2 (CH_2-N), 109.6, 110.4, 110.5, 111.1, 120.2, 122.9, (C_{arom}-H), 129.9, 131.0 (C_{arom}-C),

147.8, 148.6, 148.9, 152.8 (C_{arom}-O) and 197.5 (CO)(Found: C, 67.3; H, 7.5; N, 3.9. $C_{21}H_{27}O_5N$ requires C, 67.55; H, 7.3; N, 3.75%).

1,2-*bis*-(3,4-*Dimethoxyphenyl*)-2-*propen*-1-*one* **5e** (55%), m.p. 85-87°C(ethanol)(Lit.[7a] 85-87°C(methanol)), R_f(hexane-EtOAc, 1:1) 0.9; ν_{max} 1650 (C=O); δ_H 3.86 (3H, s, MeO), 3.88 (3H, s, MeO) 3.89 (6H, s, MeO) 5.47 (1H, s, $=CH_aH_b$), 5.91 (1H, s, $=CH_aH_b$), 6.82 (1H, d, *J* 8.1, H-5'$_{arom}$), 6.84 (1H, d, *J* 8.4, H-5"$_{arom}$), 6.96 (1H, dd, *J* 8.4, *J* 1.8, H-6"$_{arom}$), 6.99 (1H, d, *J* 1,8, H-2"$_{arom}$), 7.51 (1H, d, *J* 2.1, H-2'$_{arom}$) and 7.55 (1H, dd, *J* 8.1, *J* 2.1, H-6'$_{arom}$); δ_C 55.9, 56.1 (MeO), 109.6, 109.8, 111.1, 111.3 (C_{arom}-H), 117.3 (=CH_2), 119.7, 125.7 (C_{arom}-H), 129.9, 130.0 (C_{arom}-C), 147.9, 148.9, 149.4 (C_{arom}-O), 153.5 (*C*=CH_2), 196.6 (CO)(Found: C, 69.3; H, 6.1. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.15%).

Conjugate addition with R_2NH/Alumina.

3-*(N,N-Dimethylamino)*-1,2-*bis*-(3,4-*dimethoxyphenyl)propan*-1-*one* **2e**. Typical procedure. Neutral alumina (0.2 g) and 40% aqueous dimethylamine (5 ml) were added to a stirred solution of enone **5e** (1 g, 3 mmol) in toluene at room temperature. After stirring overnight the solvent was removed *in vacuo* and the same work-up reported above for LAH reductions was applied to afford the β-aminoketone **2e** (1.12 g, 99%) as a colourless oil.

When the same procedure was performed on enone **5e** (1 g, 3 mmol) now employing 40% aqueous pyrrolidine (5 ml) as reagent and 0.2 g of neutral alumina, 1.21 g (99%) of 1,2-*bis*-(3,4-*dimethoxyphenyl*)-3-(N,N-*pyrrolidinyl)propan*-1-*one* **2f** was isolated as a colourless oil, R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1690 (C=O); δ_H 1.70-1.74 (4H, m, 2×CH_2-CH_2N), 2.49-2.52 (4H, m, 2×CH_2-CH_2N), 2.77 (1H, dd, *J* 12.3, *J* 4.6, CH-CH_aH_b-N), 3.50 (1H, dd, *J* 12.3, *J* 9.0, CH-CH_aH_b-N), 3.82 (3H, s, MeO), 3.86 (3H, s, MeO), 3.90 (6H, s, MeO), 4.82 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 6.75-6.91 (4H, m, H_{arom}), 7.57 (1H, d, *J* 1.9, H-2'$_{arom}$) and 7.78 (1H, dd, *J* 8.4, *J* 1.9, H-6'$_{arom}$); δ_C 23.3 (C-2$_{pyrrolidine}$), 51.7 (*C*H-CO), 54.4 (C-1$_{pyrrolidine}$), 55.7, 55.8, 55.9 (OMe), 59.3 (CH_2-N), 109.4, 110.6, 111.2, 117.2, 120.4, 123.2 (C_{arom}-H), 129.6, 131.0 (C_{arom}-C), 148.0, 148.8, 149.1, 153.1 (C_{arom}-O) and 197.5 (CO)(Found: C, 69.2; H, 7.3; N, 3.7. $C_{23}H_{29}O_5N$ requires C, 69.15; H, 7.3; N, 3.5%).

Conjugate reduction with LAH/Alumina.

1,2-*Diphenyl*-3-*(N,N-dimethylamino)propan*-1-*one* **2d**. Solid enaminoketone **4d** (0.23 g, 0.9 mmol) was added to an ice-cooled stirred suspension of LAH (0.15 g, 4 mmol) in dry THF (50ml) under nitrogen. After stirring overnight, neutral alumina (0.4 g) was added, followed by 40% aqueous dimethylamine (0.25 ml). Stirring at room temperature continued for 3 days, the mixture was cooled to 0°C, ethyl acetate (7 ml) added dropwise and then water (7 ml). The same work-up reported above for LAH reductions afforded the β-aminoketone **2d** (0.22 g, 96%).

The same procedure performed on enaminoketone **4e** (1.5 g, 4.1 mmol) gave a 97% of 3-*(N,N-dimethylamino)*-1,2-*bis*-(3,4-*dimethoxyphenyl)propan*-1-*one* **2e**.

Conjugate reduction with LAH-CuI.

1,2-*bis*-*(3,4-dimethoxyphenyl)*-2-*propen*-1-*one* **5e**. Typical procedure. LAH (0.08 g, 2 mmol) was added to a stirred slurry of CuI (0.1g, 0.5 mmol) in dry THF (50 ml) at 0°C under nitrogen and a deep black colour was immediately observed with gas evolution. After stirring for 3 minutes, enaminoketone **4e** (0.2 g, 0.5 mmol) was added and allowed to react for 5 minutes. Then, ethyl acetate (5 ml) was added slowly, followed by water (5 ml). The mixture was filtered and the solid was washed with diethyl ether. The filtrate and the combined diethyl ether solutions were dried over anhydrous sodium sulfate and evaporated to afford propenone **5e** (0.17 g, 99%).

The same procedure on enaminoketone **4d** (0.2 g, 0.8 mmol) gave a 98% of 1,2-*diphenylpropen*-1-*one* **5d**.

Conjugate reduction with LAH-CuI / Alumina.

1,2-*Diphenyl*-3-*(N,N-dimethylamino)propan*-1-*one* **2d**. In the same manner as described above, enaminoketone **4d** (0.13 g, 0.5 mmol) was added to a stirred slurry of CuI (0.1 g, 0.5 mmol) and LAH (0.08 g, 2 mmol). After 30 minutes, neutral alumina (0.26 g) and 40% aqueous dimethylamine (0.25 ml) were added and allowed to react at room temperature for 3 days. The same work-up reported above for LAH reductions afforded the β-aminoketone **2d** (0.12 g, 97%).

The same procedure applied to enaminoketone **4e** (0.2 g, 0.8 mmol) afforded a 98% of 3-*(N,N-dimethylamino)*-1,2-*bis*-*(3,4-dimethoxyphenyl)propan*-1-*one* **2e**.

Mannich reaction with the tandem Me_2NH / Alumina.

3-*(N,N-dimethylamino)*-2-*(3,4-dimethoxyphenyl)*-1-*(2,3,4-trimethoxyphenyl)propan*-1-*one* **2k**. Typical procedure. Paraformaldehyde (0.02 g, 0.19 mmol) and dimethylamine hydrochloride (0.015 g, 0.19 mmol) were added to a stirred solution of deoxybenzoin **3k**[14] (0.05 g, 0.14 mmol) in ethanol (50 ml). The mixture was refluxed for 1h, and 40% aqueous dimethylamine (0.5 ml) added dropwise. After refluxing for 2h and cooling, neutral alumina (0.1 g) and 40% aqueous dimethylamine (0.25 ml) were added and allowed to react at room temperature for 3 days. The mixture was filtered and the filtrate evaporated under reduced pressure. The same work-up reported above for LAH reductions afforded the β-aminoketone **2k** (0.04 g, 65%) as a colourless oil, R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1685 (C=O); δ_H 2.26 (6H, s, NMe), 2.54 (1H, dd, *J* 12.3, *J* 4.6, CH_aH_b-N), 3.25 (1H, dd, *J* 12.3, *J* 9.0, CH_aH_b-N), 3.81 (3H, s, MeO), 3.82 (3H, s, MeO), 3.83 (3H, s, MeO), 3.84 (3H, s, MeO), 3.85 (3H, s, MeO), 4.85 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 6.60-6.9 (4H, m, H_{arom}) and 7.3 (1H, d, *J* 8.8, H-6'$_{arom}$)(Found: C, 65.3; H, 7.6; N, 3.3. $C_{22}H_{29}O_6N$ requires C, 65.5; H, 7.55; N, 3.45%).

The same procedure on diarylketones **3d,e,g,h,i** and **j**[14] (0.5 mmol scale reactions) gave the following β-aminoketones **2d,e,g,h,i** and **j**:

1,2-*diphenyl*-3-*(N,N-dimethylamino)propan*-1-*one* **2d** (87%).

3-*(N,N-dimethylamino)*-1,2-*bis*-*(3,4-dimethoxyphenyl)propan*-1-*one* **2e** (70%).

2-*(4-benzyl*-3-*methoxyphenyl)*-3-*(N,N-dimethylamino)*-1-*(3,4-dimethoxyphenyl)propan*-1-*one* **2g** (60%) as a brown oil, R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1680 (C=O); δ_H 2.28 (6H, s, NMe), 2.55 (1H, dd, *J* 12.3, *J* 4.6, CH_aH_b-N), 3.30 (1H, dd, *J* 12.3, *J* 9.0, CH_aH_b-N), 3.86 (3H, s, MeO), 3.89 (3H, s, MeO), 3.90 (3H, s, MeO), 4.80 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 5.08 (2H, s, CH_2-Ph), 6.79-7.00 (4H, m, H_{arom}), 7.30-7.40 (5H, m, H_{arom}-Bn), 7.55 (1H, d, *J* 1.9, H-2'$_{arom}$) and 7.64 (1H, dd, *J* 8.4, *J* 1.9, H-6'$_{arom}$)(Found: C, 74.6; H, 7.2; N, 3.3. $C_{27}H_{31}O_4N$ requires C, 74.8; H, 7.2; N, 3.25%).

2-*(2-bromo*-4,5-*dimethoxyphenyl)*-3-*(N,N-dimethylamino)*-1-*(3,4-dimethoxyphenyl)propan*-1-*one* **2h** (25%) as a brown oil, R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1675 (C=O); δ_H 2.31 (6H, s, NMe), 2.45 (1H, dd, *J* 12.3, *J* 4.6, CH_aH_b-N), 3.19 (1H, dd, *J* 12.3, *J* 9.0, CH_aH_b-N), 3.77 (3H, s, MeO), 3.80 (3H, s, MeO), 3.82 (3H, s, MeO), 3.84 (3H, s, MeO), 5.24 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 6.75-7.12 (3H, m, H_{arom}), 7.58 (1H, d, *J* 1.9, H-2'$_{arom}$) and 7.71 (1H, dd, *J* 8.4, *J* 1.9, H-6'$_{arom}$)(Found: C, 55.6; H, 5.8; N, 3.3; Br, 17.5. $C_{21}H_{26}O_5NBr$ requires C, 55.75; H, 5.8; N, 3.1%).

3-*(N,N-dimethylamino)*-1-*(3,4-dimethoxyphenyl)*-2-*(3,4,5-trimethoxyphenyl)propan*-1-*one* **2i** (60%) as an amber oil, R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1690 (C=O); δ_H 2.26 (6H, s, NMe), 2.53 (1H, dd, *J* 12.3, *J* 4.6, CH_aH_b-N), 3.36 (1H, dd, *J* 12.3, *J* 9.0, CH_aH_b-N), 3.77 (3H, s, MeO), 3.80 (3H, s, MeO), 3.83 (3H, s, MeO), 3.89 (3H, s, MeO), 3.90 (3H, s, MeO), 4.72 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 6.53 (1H, s, H-2"$_{arom}$ or H-6"$_{arom}$), 6.54 (1H, s, H-6"$_{arom}$ or H-2"$_{arom}$), 6.84 (1H, d, *J* 1.9, H-2'$_{arom}$), 7.58 (1H, d, *J* 8.4, H-5'$_{arom}$) and 7.65 (1H, dd, *J* 8.4, *J* 1.9, H-6'$_{arom}$)(Found: C, 65.6; H, 7.5; N, 3.3. $C_{22}H_{29}O_6N$ requires C, 65.5; H, 7.25; N, 3.45%).

3-*(N,N-dimethylamino)*-1-*(2,3-dimethoxyphenyl)*-2-*(3,4-dimethoxyphenyl)propan*-1-*one* **2j** (61%) as a colourless oil, R_f(CH_2Cl_2-EtOAc, 9:1) 0.1; ν_{max} 1680 (C=O); δ_H 2.25 (6H, s, NMe), 2.53 (1H, dd, *J* 12.3, *J* 4.6, CH_aH_b-N), 3.32 (1H, dd, *J* 12.3, *J* 9.0, CH_aH_b-N), 3.80 (3H, s, MeO), 3.84 (3H, s, MeO), 3.88 (6H, s, MeO), 4.72 (1H, dd, *J* 9.0, *J* 4.6, CH-CO), 6.73-6.89 (4H, m, H_{arom}), 7.53 (1H, d, *J* 8.3, H-4'$_{arom}$ or H-5'$_{arom}$) and 7.63 (1H, dd, *J* 8.4, *J* 1.9, H-6'$_{arom}$)(Found: C, 67.6; H, 7.5; N, 3.7. $C_{21}H_{27}O_5N$ requires C, 67.55; H, 7.3; N, 3.75%).

The same procedure on phenolic ketone **3l**[14] gave a 92 % of 3-*(N,N-dimethylaminomethyl)*-7,8,3',4'-*tetramethoxyisoflavanone* **6**, m.p. 126-127°C (ethanol)(Lit.[7a] 125-127°C), R_f(CH_2Cl_2-EtOAc, 9:1) 0.3; ν_{max} 1670 (C=O); δ_H 2.12 (6H, s, NMe), 2.65 (1H, d, *J* 13.7, CH_aH_b-N), 3.18 (1H, d, *J* 13.7, CH_aH_b-N), 3.80 (6H, s, MeO), 3.84 (3H, s, MeO), 3.85 (3H, s, MeO), 4.74 (1H, d, *J* 12.4, H-2$_{eq}$), 5.21 (1H, d, *J* 12.4, H-2$_{ax}$), 6.56 (1H, d, *J* 8.9, H-6$_{arom}$), 6.76 (1H, d, *J* 8.4, H-5'$_{arom}$), 7.01 (1H, d, *J* 2.2, H-2'$_{arom}$), 7.11 (1H, dd, *J* 2.2, *J* 8.4, H-6'$_{arom}$) and 7.66 (1H, d, *J* 8.9, H-5$_{arom}$); δ_C 47.6 (NMe_2), 52.3 (C-3), 55.7, 55.8, 56,1, 61.0 (MeO), 64.5 (C-2), 71.8 (CH_2-N), 105.5, 110.3, 110.9 (C_{arom}-H), 115.4 (C_{arom}-C), 119.1 (C_{arom}-H), 123.9, 129.2 (C_{arom}-C), 136.3, 148.4, 148.8, 154.7 (C_{arom}-O), 158.3 (C_{arom}-H), 192.4 (CO)(Found: C, 65.6; H, 6.8; N, 3.7. $C_{22}H_{27}O_6N$ requires C, 65.8; H, 6.8; N, 3.5%).

When the same procedure was performed on diarylketone **3e**[14] (1 g, 3.2 mmol) using 40% aqueous pyrrolidine as reagent, 0.89 g (70%) of *1,2-bis-(3,4-dimethoxyphenyl)-3-(N-pyrrolidinyl)propan-1-one* **2f** was isolated as a colourless oil.

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