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Three-component one-pot synthesis of functionalised (*Z*)-4-benzylidene (and alkenylidene) pyrrolidines

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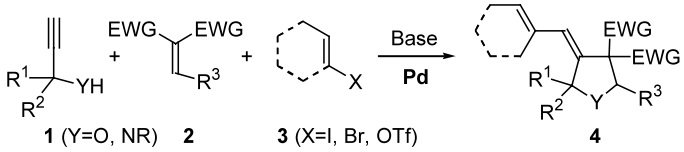
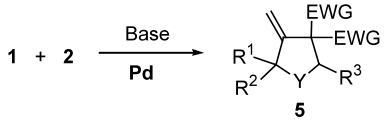
Abstract—A three-component synthesis of stereodefined 4-benzylidene-(or alkenylidene)-pyrrolidines from simple, readily available starting materials is described. This one-pot process is initiated by a conjugate addition of a propargylamine to a *gem*-diactivated olefin subsequently followed by a carbopalladation involving an aryl halide (or vinyl triflate).

In recent years, an intense interest in the development of new multicomponent reactions has arisen due to their ability to generate molecular complexity and diversity in a minimum number of steps. These reactions are therefore ideally suited for generating libraries of small molecules and particularly druglike heterocyclic compounds.[1] As part of our research program directed at developing transition metal-mediated multicomponent processes, we recently reported a three-component synthesis of highly substituted 3-(4)-benzylidenetetrahydrofurans using equimolar quantities of readily available propargyl alcohols, aryl halides (and vinyl triflates), and *gem*-diactivated olefins (Eq. (1)). The methodology was based on a cascade conjugate addition–carbopalladation sequence.[2] Adjustment of the reaction conditions was made so as to avoid any recovery of excess reagents and, most importantly, to inhibit the competitive formation of 3-(4)-methylene tetrahydrofurans as side products (Eq. (2)). We now report the results of our recent efforts devoted to the synthesis of pyrrolidines based on this methodology. These compounds are indeed of special interest due to the large number of biologically active compounds containing this moiety.[3]



1 (Y=O, NR) **2** **3** (X=I, Br, OTf) **4** (1)



5 (2)

Preliminary assays to gauge the possibility of adapting the process to the use of propargylamines as conjugate donors were conducted with the commercially available *N*-methylpropargylamine (**1a**). When **1a** was reacted with equimolar amounts of dimethyl benzylidene malonate (**2a**) and iodobenzene (**3a**) under conditions similar to those previously applied to propargyl alcohols (1.1 equiv. *n*-BuLi, 5 mol% $PdCl_2(PPh_3)_2$, THF–DMSO, rt, 3 h), the expected pyrrolidine **4a** was indeed obtained after aqueous workup and silica gel chromatography, albeit in a disappointing 27% isolated yield. Substantial amounts of the reactants were found at the end of the reaction (GC analysis), a problem that could not be solved by means of longer reaction times. In prospect of possible combinatorial applications, the ideal situation would be to avoid tedious and time-consuming purifications. Propargylamines may be easily removed by aqueous washes, and conjugate acceptors by scavenging techniques.[4] However, removal of aryl halides and vinyl triflates clearly relies on chromato-

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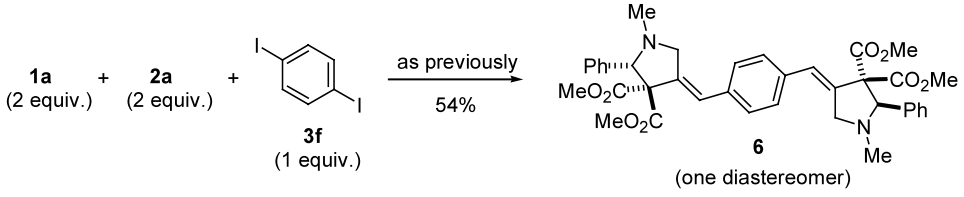
graphic purifications. It was thus decided to revisit the parameters of the reaction so as to bring it to completion or at least limit the amount of unreacted iodobenzene. The most significant results of this study are summarised in Table 1.

Gratifyingly, we found that substitution of *n*-BuLi for NaH had a dramatic effect on the kinetics of the reaction. Within the same period of time as previously allotted (3 h), only small amounts of iodobenzene remained unreacted and the yield of **4a** was raised to 61% (Table 1, entry 2). As expected, the use of excesses of both the propargylamine and the conjugate acceptor had also a beneficial effect on the yield of **4a** (up to 85%), with the aryl iodide being entirely consumed (Table 1, entries 4, 5). However, with large excesses of these reagents (>1.1 equiv.), we began to observe the formation of significant amounts of the unwanted 4-methylene pyrrolidine analogue **5a**[5] which unfortunately exhibited a similar polarity to that of **4a**. As regards the ease of purification, best results were thus obtained using only a slight excess (1.1 equiv.) of these reactants. Under these conditions, **4a** could be obtained in satisfactory purity by simple aqueous workup and filtration of the crude product through a short pad of silica gel. Alternatively, conventional chromatography afforded analytically pure **4a** in 65% yield (Table 1, entry 4).

The new reaction conditions were then applied to a series of propargylamines, aryl halides (or vinyl triflates), and *gem*-diactivated olefins in order to probe the scope and limitations of the three-component reaction (Table 2).[6] The reaction showed promising structural flexibility with respect to each component. *N*-alkyl propargylamines **1a**,**b** participated in the reaction whereas *N*-tosyl, *N*-Boc, and *N*-benzyl protected amines were essentially unreactive. All benzylidene and alkylidene malonates tested gave satisfactory results except for *p*-nitrophenyl derivative **2e** which led to inseparable mixtures of pyrrolidines **4** and **5** (Table 2, entries 5 and 8). It is worth noting that the reaction opens access to potentially interesting nicotine derivatives (Table 2, entry 2). The reactivity of olefins bearing activating groups other than esters was also investigated. Inclusion of a sulfonyl or nitro moiety in these reactants was of particular interest as it was anticipated from previous work that the resulting cyclised products could be functionalised further by allylic substitution.[7] Disappointingly, as exemplified by the reaction of ethyl 2-phenylsulfonyl cinnamate (**2g**) (Table 2, entry 7), poor results were obtained with vinyl sulfones. On the other hand, nitroolefins, e.g. 1-nitrocyclohexene and β-methyl-β-nitrostyrene, gave complex mixtures of uncharacterised products. We also attempted to react commercially available ethyl 2-cyanocinnamate and benzylidene malononitrile, but these starting materials furnished preferably the two-component cycloaddition products **5**.

In another experiment we succeeded in assembling five reactants by using 1,4-diodobenzene (**3f**) as a biscoupling species. Thus, reaction of **3f** with two equivalents of the sodium salt of **1a** and two equivalents of **2a** yielded the symmetrical product **6** resulting from two conjugate addition–carbopalladation processes. Four C–C and two C–N bonds were created in a single operation. Compound **6** was isolated in 54% yield as a single diastereomer, presumably the *meso* form,[8] as depicted in Eq. (3).



(3)

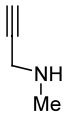
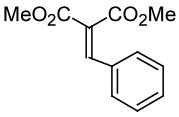
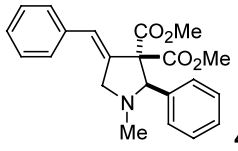
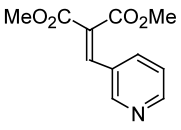
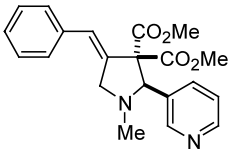
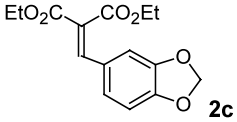
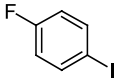
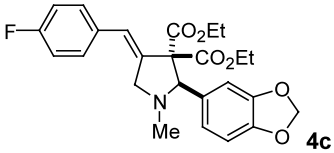
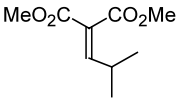
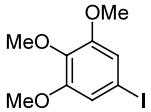
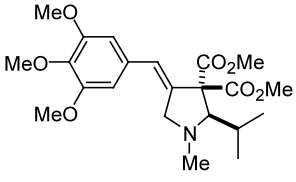
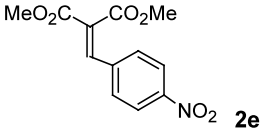
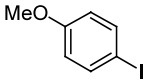
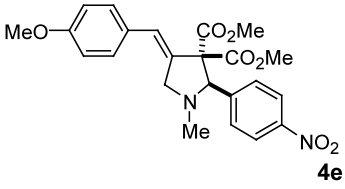
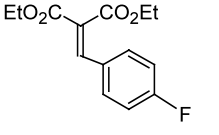
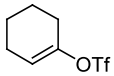
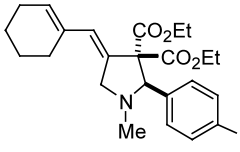
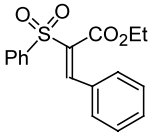
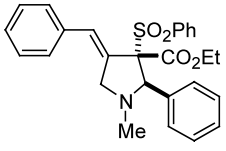
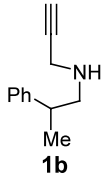
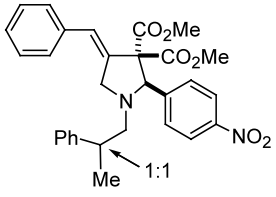
In conclusion, we have shown that a series of hitherto unknown 4-benzylidene (and alkenylidene) pyrrolidines can be assembled from readily available, when not commercially disposable, starting materials. The one-

Table 1. Reaction of *N*-methylpropargylamine (**1a**) with dimethyl benzylidene malonate (**2a**) and phenyl iodide (**3a**) to yield **4a**

Entry	Ratio **1a**:**2a**:**3a**	Base	Solvent	Time (h)	Yield (%)[a]
1	1:1:1	*n*-BuLi	THF–DMSO (3–2)	3	27[b]
2	1:1:1	NaH	THF–DMSO (3–2)	3	61[b]
3	1:1:1	NaH	THF	4	35[b,c]
4	**1.1:1.1:1**	**NaH**	**THF–DMSO (3–2)**	**3**	**65**
5	1.5:1.5:1	NaH	THF–DMSO (3–2)	2.5	85[c]

[a] Isolated yields calculated with respect to the quantities of iodobenzene introduced in the reaction.
[b] Reaction was not complete.
[c] Small amounts (ca. 5–10%) of the corresponding 4-methylene pyrrolidine **5** were isolated as side product.

Table 2. Three-component synthesis of 4-benzylidene (and alkenylidene) pyrrolidines[a]

Entry	Propargyl amine	Activated olefine	Unsaturated halide (or triflate)	Product [b]	Yield (%) [c]
1	 **1a**	 **2a**	 **3a**	 **4a**	65
2	”	 **2b**	”	 **4b**	75
3	”	 **2c**	 **3b**	 **4c**	81
4	”	 **2d**	 **3c**	 **4d**	60
5	”	 **2e**	 **3d**	 **4e**	50 (+**5e**, 15%)[d]
6	”	 **2f**	 **3e**	 **4f**	70
7	”	 **2g**	**3a**	 **4g**	37[e]
8	 **1b**	**2e**	”	 **4h**	37 (+**5h**, 9%)[d]

[a] All reactions were performed on a 1 mmol scale.

[b] One enantiomer drawn.

[c] Isolated yields.

[d] A mixture of inseparable pyrrolidines **4** and **5** was obtained. Yields were determined by ^{1}H NMR analysis.

[e] 16% of the corresponding 4-methylene pyrrolidine **5** was isolated as side product.

pot three-component reaction described herein complements our previous results obtained with propargyl alcohols. It operates most efficiently with *N*-alkylpropargylamines, the alkyl group thereby introducing an additional element of diversity.

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6. Representative procedure for the three-component reaction. Synthesis of dimethyl 4-benzylidene-1-methyl-2-phenyl-pyrrolidine-3,3-dicarboxylate (**4a**). *n*-BuLi (2.0 M in hexanes, approx. 50 μL, 0.1 mmol) was added dropwise to a well stirred suspension of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) in DMSO (2 mL) under a nitrogen atmosphere until a dark red homogeneous solution was obtained. In a separate flask, *N*-methylpropargylamine (76 mg, 1.1 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 44 mg, 1.1 mmol) in THF (3 mL) under a nitrogen atmosphere. The solution was stirred at rt for 10 min and then successively treated with dimethyl benzylidene malonate (220 mg, 1.1 mmol), iodobenzene (204 mg, 1.0 mmol), and the freshly prepared palladium complex solution. The reaction mixture was stirred at rt for 3 h and after usual workup with aqueous $NaHCO_3$ solution and dichloromethane, the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (silica gel; ethyl acetate/petroleum ether) to afford pyrrolidine **4a** (237 mg, 65%) as a solid. Mp 138–139°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.25 (m, 10H), 6.75 (s, 1H), 4.46 (s, 1H), 4.26 (dd, $J=13.7$ and 1.7 Hz, 1H), 3.81 (s, 3H), 3.38 (dd, $J=13.7$ and 1.7 Hz, 1H), 3.21 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 169.1, 137.5, 137.1, 136.5, 128.7, 128.4, 128.1, 128.0, 126.9, 76.4, 75.1, 70.8, 59.8, 53.0, 52.2, 40.5. Anal. calcd for $C_{22}H_{23}NO_4$; C, 72.31; H, 6.34; N, 3.84. Found C, 72.16; H, 6.38; N, 3.84%.
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8. Selected data for compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, $J=6.6$ Hz, 4H), 7.40–7.25 (m, 10H), 6.76 (s, 2H), 4.48 (s, 2H), 4.30 (d, $J=13.9$ Hz, 2H), 3.83 (s, 6H), 3.41 (d, $J=13.9$ Hz, 2H), 3.23 (s, 6H), 2.29 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 169.4, 137.8, 137.1, 136.3, 129.0, 128.8, 128.4, 126.9, 75.5, 71.2, 60.2, 53.4, 52.5, 40.9. HRMS: calcd for $C_{38}H_{40}N_2O_8$ (MH^+) 653.2863; found 653.2861.