A Simple One-pot Organometallic Formylation/Trapping Sequence Using *N*-Formylcarbazole

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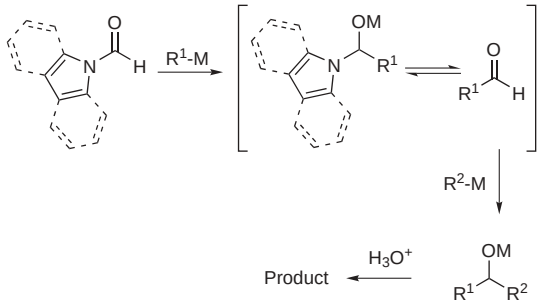
Abstract: Treatment of a range of sp^3-, sp^2- and sp-nucleophiles with *N*-formyl carbazole leads to the formation of the metastable anionic carbazole carbinols. In the presence of a second nucleophilic reagent such as phosphonoacetate or an organolithium, these collapse on warming to the aldehyde which is trapped in situ to afford the α,β-unsaturated esters or secondary carbinols respectively.

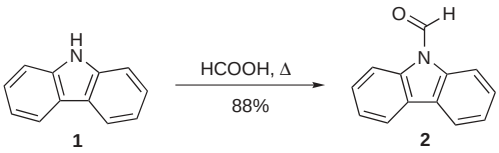
Key words: carbinols, enynes, formylation, heterocycles, *N*-formylcarbazole

Methods for the formylation of organometallic reagents[1,2] have received much attention over the years due to the obvious synthetic utility of the one carbon homologation procedure and the wealth of reactions possible with the aldehyde product.[3,4] For sp^3-, sp^2- or sp-carbanions, the formylating agent is invariably based around an *N*-formylated amine, which is not only reactive towards the organometallic, but the resulting anionic carbinol is stable until dilute acidic work-up and only then is the aldehyde released. Reports by our group[5] and others[6] have revealed that while *N*-carbinols of pyrrole are stable in their neutral state, they may be collapsed back to the parent carbonyl compound under basic conditions. This metastability lends itself to the possibility of a one-pot multicomponent formyl transfer/aldehyde trapping procedure[7,8] using *N*-formyl heterocycles as the reagent (Scheme 1) and herein we wish to report our findings.



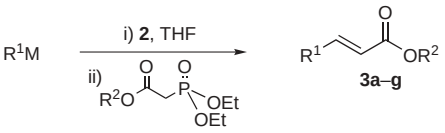
Scheme 1

Initially, *N*-formylpyrrole and *N*-formyl-3-methylindole were considered as potential candidates. However in the former case, synthesis was a major set-back and in the latter, the unpleasant odour associated with the skatole starting material focused our attention on other formylation sources. *N*-Formylcarbazole **2** was subsequently identified as the reagent of choice. The parent heterocycle is cheap and the synthesis can be efficiently carried out on a large scale by simply boiling carbazole **1** in formic acid for 8 hours and the product is isolated by crystallization (Scheme 2).[9]



Scheme 2

With multigram quantities of *N*-formylcarbazole **2** in hand, the sequential formylation/aldehyde trapping sequence was investigated. The addition of a range of nucleophiles to **2** was carried out at –78 °C, followed by the addition of Wadsworth–Horner–Emmons reagent. The resulting α,β-unsaturated esters were obtained in reasonable to good yields over the two steps (Scheme 3, Table 1, General Procedure A).



Scheme 3

Table 1 One-pot Organometallic Formylation and Wadsworth–Horner–Emmons Reaction (General Procedure A)

Entry	R^1M	R^2	Product	Yield (%)	*E*:*Z*
1	*n*-BuLi	Et	**3a**	82	25:1
2	*n*-BuLi	*t*-Bu	**3b**	71	15:1
3	*n*-BuLi	Bn	**3c**	79	24:1
4	*s*-BuLi	Et	**3d**	50	14:1
5	*i*-PrMgCl	Bn	**3e**	46	>50:1
6	*i*-PrMgBr	Bn	**3f**	45	29:1
7	PhLi	Bn	**3g**	68	>50:1

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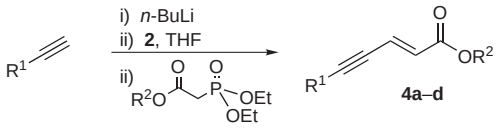
It was pleasing that both aliphatic and aromatic organometallic nucleophiles could be used in these reactions (entries 1–6 vs. entry 7) and that moderate to high yields of the product could be obtained, irrespective of the nature of the Wadsworth–Horner–Emmons reagent used (entries 1–3).

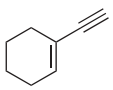
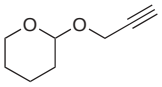
More specifically, of the α,β-unsaturated esters, good yields were obtained when primary alkyl lithium and phenyl lithium reagents were used (entries 1–3 and 7). With secondary alkyl lithiums and secondary Grignard reagents, the yields were somewhat lower, but still acceptable (entries 4–6). The diminished yields presumably arose from competing proton transfer reactions.

To circumvent this problem and enhance the scope of the reaction, alkynyl lithium reagents were explored in the sequential formylation/WHE reaction (Scheme 4, Table 2).



Scheme 4

Table 2 Enyne Synthesis (General Procedure B)

Entry	Substrate	R^1	Product	Yield (%)	*E*:*Z*
1		Et	**4a**	90	30:1
2		Et	**4b**	100	>50:1
3		Et	**4c**	89	>50:1
4		Bn	**4d**	65	30:1

As anticipated, enyne formation[10,11] proceeded in good to excellent yield for both simple (entries 1, 2) and functionalized (entries 3, 4) alkynes (General Procedure B).

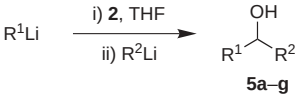
While these products **4a**–**d** allow scope for further functionalization, we were keen to investigate other nucleophilic addition reactions to the in situ generated aldehyde.

To test that the addition of a second organolithium to the crude aldehyde could proceed smoothly, three alkyne dimerization reactions were carried out, and pleasingly, the products were isolated in good to excellent yields (Table 3, entries 1–3). The dialkyne motifs are frequently found in natural product compounds and synthetic intermediates thereof.[12,13]

There is no doubt that this procedure would work equally well using ethyl formate as the one carbon electrophile. However the overwhelming advantage of the *N*-formylcarbazole approach lay in the metastability of the intermediate metal alkoxide, such that with appropriate control, it was envisaged possible to give the mixed product in high selectivity, in contrast to the statistical 1:2:1 mixture anticipated with traditional formylating agents.

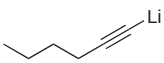
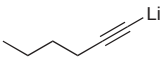
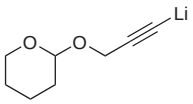
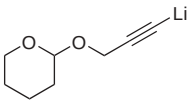
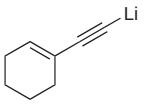
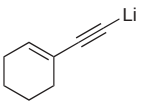
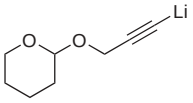
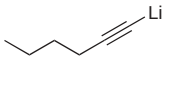
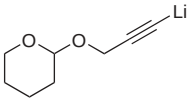
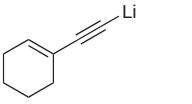
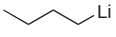
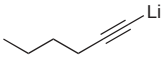
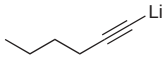
Upon optimization, the protocol led to formation of the desired mixed dialkynes in greater than 10:1 selectivity over the undesired symmetrical dialkynes and the products were isolated in good yields (Table 3, entries 4 and 5).

To further demonstrate the scope of this method, sp^3- and sp^2- nucleophiles were also used in unsymmetrical product formation (entries 6 and 7). The consistently good yields obtained suggest the method should be general for a wide range of organometallic reagents (Scheme 5).



Scheme 5

Table 3 Aldehyde Trapping with a Second Organolithium (General Procedure C)

Entry	R^1	R^2	Product	Yield (%)
1			**5a**	67
2			**5b**	74
3			**5c**	70
4			**5d**	67
5			**5e**	71
6			**5f**	81
7			**5g**	70

In summary, we have demonstrated the utility of readily prepared *N*-formylcarbazole as a reagent for a novel sequential formylation and aldehyde trapping procedure. This has been illustrated in the one-pot synthesis of α,β-unsaturated esters as well as symmetrical and unsymmetrical carbinols by sequential addition of a first, then a second carbon centered nucleophile. Further work directed

towards extending the scope of this procedure regarding the range of secondary nucleophiles used to trap the intermediate aldehyde is underway.

Synthesis of *N*-Formylcarbazole (2)

A mixture of carbazole (50.0g, 0.30 mol) and formic acid (375 mL) was heated under reflux overnight. Formic acid was removed by distillation. The product was recrystallized (EtOAc) to give the title compound as white crystals (44.1 g, 88%). The spectral data was in agreement with literature values.[14]

General Procedure A

To a solution of *N*-formylcarbazole (2 mmol) in THF (8 mL) at –78 °C was added the organometallic reagent (2.2 mmol). The reaction mixture was stirred for 1 h at –78 °C, then warmed to –10 °C before the addition of benzyldiethylphosphonoacetate (2.5 mmol). The reaction mixture was allowed to warm to r.t. overnight then washed with distilled H_2O and brine. The crude reaction mixture was concentrated in vacuo and purified by flash column chromatography (40–60 petroleum ether and Et_2O). The products were characterized and where relevant, confirmed by comparison with the literature.

General Procedure B

To a solution of the alkyne (2.2 mmol) in THF (5 mL) at –78 °C, was added *n*-butyllithium (2.2 mmol) and the solution stirred for 10 min before being added to a solution of *N*-formylcarbazole (2 mmol) in THF (3 mL) at –78 °C. The reaction mixture was stirred for 1 h at –78 °C then warmed to –10 °C before the addition of benzyldiethylphophonoacetate (2.5 mmol). The reaction mixture was allowed to warm to r.t. overnight, and Et_2O and H_2O were added. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, concentrated in vacuo and purified by flash column chromatography, (40–60 petroleum ether and Et_2O). The products were characterized and where relevant, compared with the literature.

General Procedure C

To a solution of *N*-formylcarbazole (2 mmol) in THF (3 mL) at –78 °C was added a –78 °C solution of the first organolithium (2 mmol) in THF (3 mL). The reaction mixture was stirred for 1 h before the addition of a –78 °C solution of the second organolithium (2 mmol) in THF (3 mL). The reaction mixture was warmed to r.t. over 3.5 h, then quenched by the addition of H_2O. The reaction mixture was diluted with 40–60 petroleum ether, then filtered through cotton wool to remove most of the carbazole, then purified by flash column chromatography (40–60 petroleum ether and Et_2O). The products were characterized and where relevant, compared with the literature.

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