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DOI: 10.1039/C8OB02282H

Organic & Biomolecular Chemistry

PAPER

C-alkylation of *N*-alkylamides with styrenes in air and scale-up using a microwave flow reactor

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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C-alkylation of *N*-alkylamides with styrenes is reported, proceeding in ambient air/moisture to give arylbutanamides and pharmaceutically-relevant scaffolds in excellent mass balance. Various amide and styrene derivatives were tolerated, rapidly affording molecular complexity in a single step; thus highlighting the future utility of this transformation in the synthetic chemistry toolbox. Reaction scalability (up to 65 g/h product) was demonstrated using a Microwave Flow reactor, as the first example of a C-alkylation reaction using styrenes in continuous flow.

Introduction

Synthesis of amides is fundamentally important in organic chemistry and particularly within active pharmaceutical ingredients (APIs).[1-5] Amide synthesis from reactions of carboxylic acids and amines involves pre-activation of the carboxylic acid[2] or generation of an activated intermediate *in situ* by use of a coupling agent.[3] Though highly versatile and general, such bond formations typically require inefficient, often expensive and hazardous reagents and generate large quantities of waste.[4] To this end, elegant catalytic methods have been recently reported for direct condensation of amines with carboxylic acids.[5,6] However, novel and scalable methods for amide synthesis are still desirable.[7] A complementary strategy is functionalization of simple amide feedstocks. Historically, functionalization of amide α-C positions is achieved *via* deprotonation employing a strong base (LDA, BuLi, see Figure 1A),[8] followed by C-alkylation, but these highly reactive bases require handing under inert atmosphere, moisture-free conditions at cryogenic temperatures. Related to this is the potassium base-mediated addition of amides (and similar compounds) to α,β-unsaturated carbonyl compounds, reported by Kobayashi *et al.*,[9] according with the natural electronics. In this context, styrenes represent an interesting, underexploited class of 'electrophile', because they are electron-rich.

Addition of premade alkyllithium compounds to styrenes is well known.[10] Pines first reported the addition of alkylpotassiums generated from alkyl-substituted heterocycles (pyridines/pyrazines/thiophenes) to styrenes and the addition of alkylpyridines to styrenes was extended in a recent report.[11] Knochel reported KO*t*Bu-mediated α-C alkylation of nitriles, imines and ketones to styrenes (Figure 1B).[12] Almost five decades ago, Pines *et al.* reported a curious KO*t*Bu-mediated transition metal-free C-alkylation of *N*-methyl-2-pyrrolidinone (NMP) or *N*-methyl-2-piperidone with styrenes, which gave rise to amide-styrene monoadducts and bisadducts depending

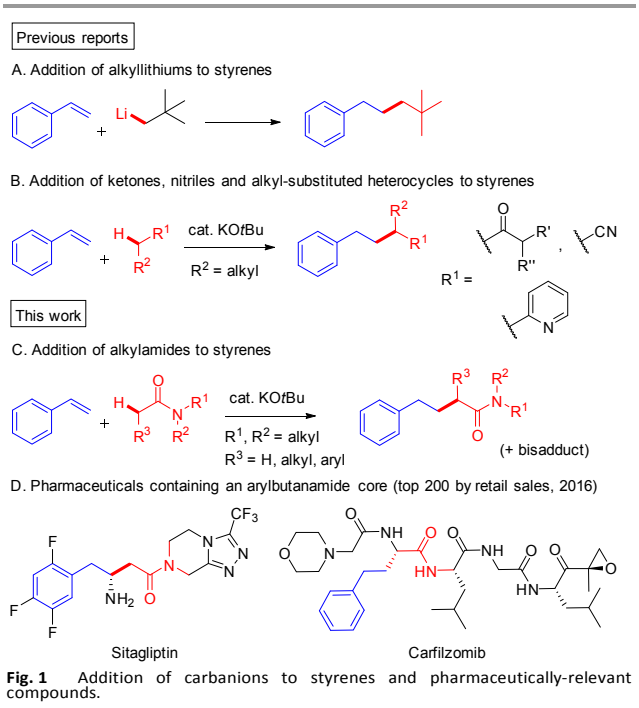

Fig. 1 Addition of carbanions to styrenes and pharmaceutically-relevant compounds.

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Electronic Supplementary Information (ESI) available: Microwave Continuous Flow Reactor details, experimental procedures and characterization data for novel compounds is provided. See DOI: 10.1039/x0xx00000x

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on the conditions employed.[13] The reaction appears to proceed via addition of a potassium amide enolate to styrene. For the two cyclic amides aforementioned, the constrained molecular geometry allows reactions to proceed compared to: i) 7-membered cyclic amide *N*-methylcaprolactam (NMC), which gave no reaction, ii) open-chain amides, which were not reported by Pines. Aside from the two cyclic amide substrates reported by Pines, this reaction has since featured merely as a low-yielding (<10%) undesired side-reaction.[12] The substrate scope of this reaction in the amide and styrene coupling partner had yet to be established. Moreover, for C-alkylations with styrenes to be industrially viable in general, they require proof of scalability yet multigram-scale and continuous flow applications have not been reported. We reasoned use of elevated reaction temperatures and additives (e.g. 18-crown-6) may increase the reactivity of the potassium enolate, allowing a wider scope of amide substrates to react. Herein, we report a versatile C-alkylation of alkylamides using styrenes (Figure 1C) proceeds under ambient air and moisture in excellent mass balance, under readily accessible conditions and is scalable up to 65 g/h in continuous flow. This method provides convenient and unique access to arylbutanamides; pharmaceutically relevant cores (present, for example, in Sitagliptin and Carfilzomib, Figure 1D).[14]

Results and discussion

Preliminary results came serendipitously from studies of a transition metal-free Heck reaction, reported by Shirakawa *et al.* (Figure 2).[15] Based on recent advancements in the mechanistic understanding of reaction classes, it is likely that the solvent, DMF, undergoes deprotonation by KO*t*Bu at elevated temperature, leading to trace amounts of carbamoyl anions which ultimately initiate radical chain reactions of haloarenes *via* single electron transfer.[16,17] We elected to examine the impact of DMA as solvent on the reaction, which is blocked to formation of the carbamoyl anion.[18] The reaction in DMA solvent gave a decreased yield of **3** (16%) compared to DMF (49%) in our hands (Figure 2), but additionally yielded **4a** and **4b**. Products **4a** and **4b** were favored by omission of EtOH and iodoarene **1**. Hence, heating a mixture of styrene and KO*t*Bu (0.6 eq.) in DMA gave **4a** (39%) and **4b** (49%) (Table 1, entry 1). Here, we realized the opportunities to exploit this curious reaction as an unconventional route to the synthesis of arylbutanamides and hence began investigating the reaction optimization. Selectivity for monoadduct **4a** was promoted by decreasing concentration of **2** to 0.50 M in DMA. The reaction was almost unaffected by running under air instead of Ar. KO*t*Am, KHMDS, NaHMDS and KOH were similarly effective whilst NaO*t*Bu, KF, K_2CO_3 and strong organic bases DBU and DABCO gave no reaction (see ESI). That KOH was equally effective as KO*t*Bu may explain reaction tolerance to ambient air/moisture, to which KO*t*Bu is sensitive. The reaction was sluggish at rt, highlighting the importance of elevated temperature for reactions of open-chain amides compared to room-temperature conditions reported by Pines. Decreasing concentration of **2** to 0.23 M in DMA gave little selectivity improvement for **4a** whilst addition of solubilizing agent 18-crown-6 drastically decreased **4a** selectivity and allowed the reaction to proceed at rt. A control reaction with 18-crown-6 only gave no reaction. Interestingly, NaO*t*Bu effected successful reaction in the presence of 18-crown-6 at 80 °C but not at rt. Control reactions (see ESI) revealed the reaction was shut down by addition of protic sources EtOH (10 eq.) or BHT (1 eq.) and was unaffected by light exclusion.

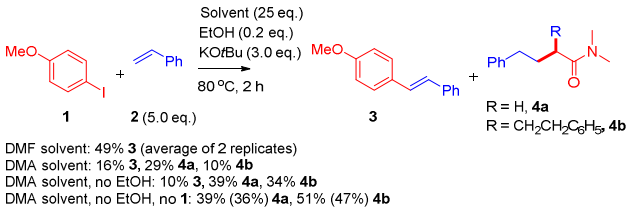
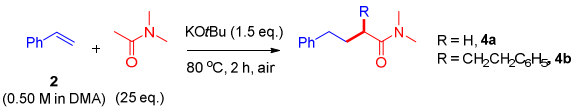


Fig. 2 Preliminary studies of a transition metal-free Heck reaction in DMF *vs.* DMA solvent and control reactions.

Table 1 Optimization of C-alkylation Reaction of DMA[a]



2 (0.50 M in DMA) (25 eq.)

Entry	Deviation from Reaction Conditions	Yield (%)[a] 4a	4b
1[b]	KO*t*Bu (0.6 eq.), 80 °C, 1.90 M **2** in DMA (4.5 eq.), under Ar	39 [36]	51 [47]
2	KO*t*Bu (0.6 eq.), 80 °C, under Ar	77	15
3	KO*t*Bu (0.6 eq.), 80 °C	71	16
4[c]	KO*t*Bu (1.5 eq.), 80 °C	72	21
5	KO*t*Bu (3.0 eq.), 80 °C	63	16
6	KO*t*Bu (1.5 eq.), rt	23	2
7[b]	KO*t*Bu (1.5 eq.), 80 °C, 0.23 M **2** in DMA (47 eq.)	75 [77]	11 [7]
8	KO*t*Bu (1.5 eq.), 80 °C, 18-crown-6 (1.5 eq.)	48	36
9	KO*t*Bu (1.5 eq.), rt, 18-crown-6 (1.5 eq.)	39	45
10	No base, 80 °C, 18-crown-6 (1.5 eq.)	0	0
11	NaO*t*Bu (1.5 eq.), 80 °C	5	0
12	NaO*t*Bu (1.5 eq.), 80 °C, 18-crown-6 (1.5 eq.)	65	9
13	NaO*t*Bu (1.5 eq.), rt, 18-crown-6 (1.5 eq.)	0	0

Unless otherwise stated, reactions were conducted using 1.15 mmol **2** (0.50 M) in DMA (25.0 eq.) and sealed under an air atmosphere. [a]Yields determined by ^{1}H NMR (isolated yields in parenthesis). [b]Yields are consistent with isolated yields, see ESI. [c]Average of 3 replicates, identified as conditions **A**.

A range of both acyclic and cyclic alkylamides were tolerated by the reaction with styrene (Figure 3), affording good to excellent yields (72 - 91%) of monoadducts under conditions **A** (Table 1, entry 4). The reaction proceeded successfully despite the potential steric hinderance provided by an α-methyl-substituent, giving excellent selectivity for monoadduct **6a** in 98% yield. When DMA was used as the amide partner reacting with different styrenes, the reaction

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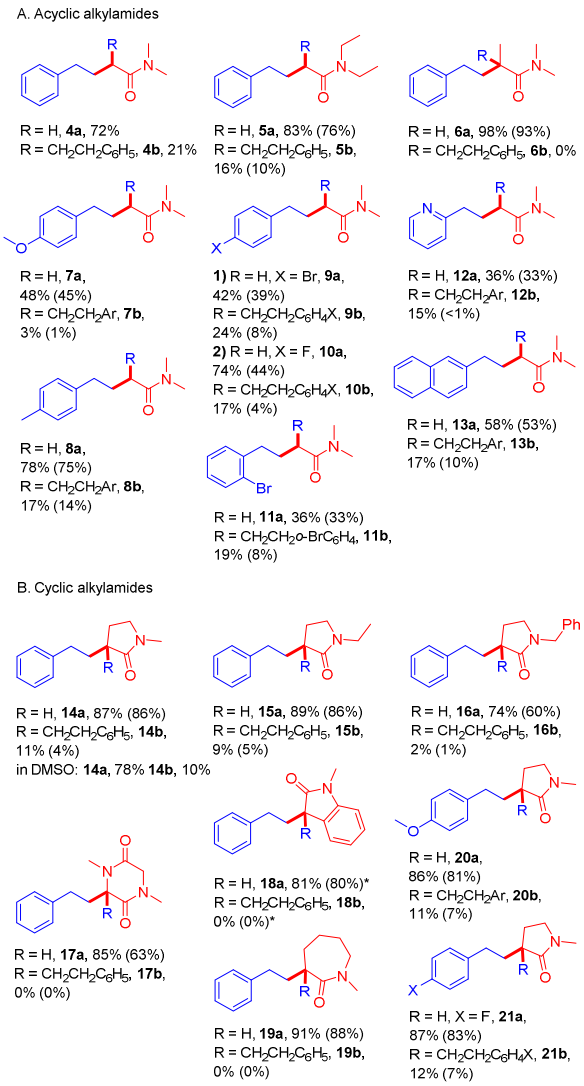

Fig. 3 Substrate scope for conditions **A** varying amide and styrene components. Isolated yields are shown in parentheses. *Reaction performed using **2** in 0.35 M DMSO and using 15 eq. of amide substrate.

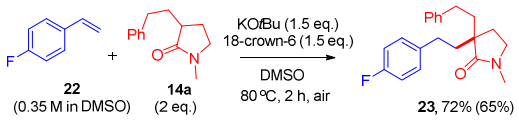

Fig. 4 Reaction of product **14a** with a different 4-fluorostyrene. Isolated yields are shown in parentheses.

appeared to be sensitive to electronic variations in the styrene. Monoadducts were observed in modest to high yields (36 - 78%), the reactions proceeded in variable mass balance (51 - 95%) and variable selectivity (1 : 0.06 to 1 : 0.60 mono- : bis-adduct). Whilst 4-vinyltoluene smoothly afforded **8a/8b**, 4-vinylanisole which is more electron-rich afforded **7a** in excellent selectivity but mass balance was only 51%. Other electron-rich styrenes, such as α-methylstyrene, β-methylstyrene (see ESI) and 4-methyl-5-vinylthiazole gave low yields or failed to afford detectable products by ^{1}H NMR. Such results are attributed to the slower desired reaction of the electron-rich styrenes and their loss to thermal polymerization. Electron-deficient styrenes afforded better mass balance, yet selectivity shifted toward bisadducts. The reaction proceeded using NMP,[13] giving rise to monoadduct (**14a**) in notably higher selectivity than reactions using DMA. Further studies revealed NMP was more reactive than DMA, and that reactions proceeded smoothly in the presence of 18-crown-6 (either with KO*t*Bu or NaO*t*Bu base) as a solubilizing agent (see ESI for full investigations, including co-solvent evaluation to allow amide equivalents to be decreased). An *N*-benzyl group was tolerated as seen in the successful formation of **16a**. Interestingly, the *N*-methyl-substituted diketopiperazine (sarcosine anhydride), oxindole and caprolactam derivatives gave excellent yields and perfect selectivity for the monoadducts **17a**, **18a** and **19a**. Notably, our conditions gave successful reaction of *N*-methylcaprolactam which gave no reaction under conditions reported by Pines.[13] A surprising and notable example was sarcosine anhydride, which potentially could form up to 5 products, yet monoadduct **17a** was afforded as the sole product. As opposed to acyclic amide DMAc, reactions of cyclic amide NMP as the amide partner were insensitive to the electronics of the styrene. Styrene, 4-methoxystyrene and 4-fluorostyrene gave **14a/14b**, **20a/20b** and **21a/21b** in almost identical yields, ratios and in >97% mass balance. Presumably, the higher reactivity of NMP relative to DMAc outcompetes deleterious side-reactions. We postulated whether the monoadduct product could be re-subjected to the reaction conditions using a different styrene partner to afford a compound with interesting 3D geometry and a differentially-substituted quaternary center. To our delight, monoadduct **14a** (2.0 eq.) reacted with 4-fluorostyrene **22** (1.0 eq.) in DMSO solvent to afford compound **23** in the presence of 18-crown-6 (1.5 eq.). Notably, the addition of 18-crown-6 increased the reactivity such that only 2.0 eq. of amide **14a** were required to obtain **23** in good yield. This is important, since the absence of 18-crown-6 necessitates high loadings of amide (15 - 25 eq.) in order for reaction completion and satisfactory yields, which is inefficient. Though the amide partners herein are readily available and inexpensive, further optimisation of conditions is necessary to decrease the amide loading for future application of this method to complex systems (Figure 1D). A challenge is that i) stoichiometric loadings of amide result in sluggish conversion ii) 18-crown-6 increases the reactivity but promotes the selectivity towards the bisadduct (see ESI for full investigations of the reaction optimisation).

We sought to demonstrate reaction scalability *via* flow processing (Table 2). Flow processing is globally recognized as a promising technology within the pharmaceutical[19-21] and fine/commodity[22] chemical industries. The NaO*t*Bu/18-crown-6 combination was found to be most suitable for flow due to solubility. In batch mode, conditions gave high selectivity for monoadduct **14a** at 80 °C but the reaction did not proceed at rt. A commercially available and previously reported microwave (MW) flow reactor was employed.[23] At rt, no reaction was observed in flow. At 140 °C, a residence time (R_T) of 3 min gave yields of **14a/14b** which matched those of the

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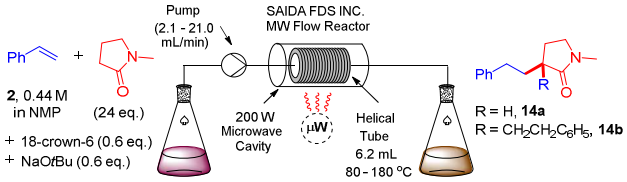
batch conditions, yet the g/h productivity was *ca*. 100 times higher in flow.[24] The optimum conditions for yield and productivity were identified; affording **14a** in 73% (64.9 g/h) and **14b** in 7% (9.4 g/h). These conditions (R_T = 0.4 min, T = 180 °C) were employed for 5 min in a multigram-scale reaction, affording 5.2 g of **14a** (70%) after work-up and isolation. Results show a remarkable increase in productivity and scalability opportunities in moving from batch to flow. MW heating allowed the elevated temperatures necessary at such short residence times to sustain high yield and bolster productivity at the reaction step. The benefits of MW towards rapid, uniform heating and expedition of reaction optimization have been previously disclosed.[23]

Table 2 Reaction Scale-up using a Microwave Flow Reactor.[a]



Entry	R_T	Temp[b]	Yield (%)[c,d]		Productivity (g/h)[e]	
[method]	(min)	(°C)	**14a**	**14b**	**14a**	**14b**
1 [B, T][f]	120	25	0	0	-	-
2 [B, T]	120	80	88	10	0.10	0.02
3 [F, MW]	3.0	25	0	0	-	-
4 [F, MW]	3.0	140	87	8	9.49	1.32
5 [F, MW]	0.4	180	73 [70]	7 [3]	64.86	9.40

[a]B, batch (**2**, 0.45 M in NMP); reaction time (min) is shown in parenthesis. T, thermal heating for 2 h reaction time (see ESI). F, flow (**2**, 0.44 M in NMP). MW, microwave heating. R_T, residence time. [b]Reaction temperature measured at the reactor tube exit upon reaching steady-state. [c]Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene (10 mol%) as an internal standard, see ESI for details. [d]Isolated yields in parentheses; 5.17 g of **14a** and 0.32 g of **14b** isolated after employing entry 5 conditions for 5.0 min. [e]Batch productivities are calculated from NMR yield and total reaction time. Flow productivities are calculated from NMR yield and flow rate. [f]1.5 eq. of NaO*t*Bu was used.

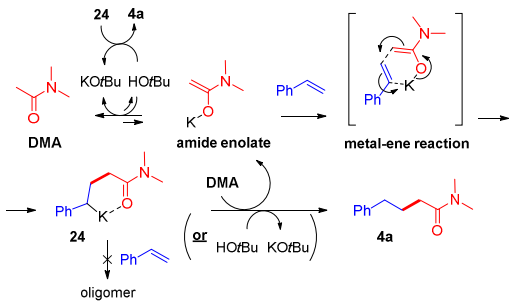


Fig. 5 Proposed reaction mechanism.

A plausible reaction mechanism is proposed in Figure 5. Deprotonation of DMA (pK_a = 29.4 in H_2O)[25] by KO*t*Bu (pK_a *t*BuOH = 16.6 in H_2O)[26] occurs via an equilibrium (heavily skewed toward reactants due to the large pK_a difference). The potassium-amide enolate reacts with the styrene via a metal-ene-type reaction to afford **24** (where alkylpotassium **24** is stabilized by an interaction with the lone pair on the carbonyl oxygen), which undergoes protonation to form monoadduct **4a**. Monoadduct **4a** reacts with a second molecule of styrene via the same mechanism to afford bisadduct **4b**. Alternatively, intramolecular proton transfer from the α-position gives a potassium enolate which enters the catalytic cycle. Addition of styrene at the benzylic position of **24** to give oligomers was not observed.[27] A radical mechanism was deemed unlikely due to the outcomes of experiments involving 1.0 eq. of radical traps TEMPO and Galvinoxyl radical (see ESI for full details).

Conclusions

We report C-alkylation of alkylamides using styrenes to give a range of pharmaceutically-relevant arylbutanamide scaffolds. This underexploited reaction rapidly builds molecular complexity, proceeds in excellent mass balance (with respect to the styrene) and generally provides monoadducts selectively and in good yield. Scalability was demonstrated in a commercially available MW flow reactor. To our knowledge, this is the first example of a C-alkylation reaction using styrenes as the 'electrophile' in flow. Further studies are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge financial support from the subsidy program for innovative business promotion of Shizuoka Prefecture, Japan SAN-Pro, the Japan Trust International Research Cooperation Project and the University of Shizuoka.

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