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A Baker-Venkataraman retro-Claisen cascade delivers a novel alkyl migration process for the synthesis of amides

Dana Ameen[1] and Timothy J. Snape[2,*]

[1] Department of Pharmaceutical Chemistry, College of Pharmacy, Hawler Medical University, Erbil 44001, Kurdistan region, Iraq.

[2] School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, PR1 2HE, UK. Tel: +44 (0)1772 895805; E-mail: tjsnape@uclan.ac.uk

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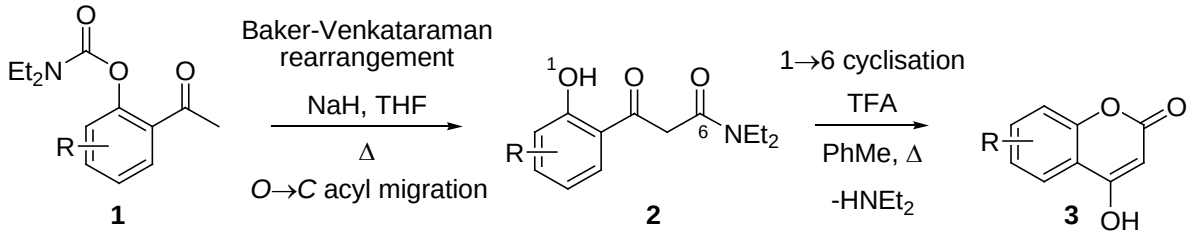
Abstract A simple extension of the carbamoyl Baker-Venkataraman rearrangement has been developed. If residual water in the reaction is not strictly excluded a Baker-Venkataraman *retro*-Claisen cascade takes place, giving amide products, in which an alkyl group apparently migrates between two functionalities of the substrate.

Acyl migrations permeate the chemical literature, yet most involve heteroatom→heteroatom rearrangements.[1] However, the specific rearrangement which sees the *O*→*C* migration of phenyl esters—the so-called Baker-Venkataraman rearrangement—has also received considerable citations in organic chemistry, especially since it can be used for the regioselective formation of carbon–carbon bonds.[1] The majority of such reactions cover examples which describe the migration of a phenyl ester from oxygen to carbon, but the first major variant of the rearrangement was reported by Snieckus, in which *ortho*-acyl arylcarbamates **1** were rapidly and efficiently converted into substituted 4-hydroxycoumarins **3** in 79-95% overall yields, via the rearrangement product **2** (Scheme 1).[2]

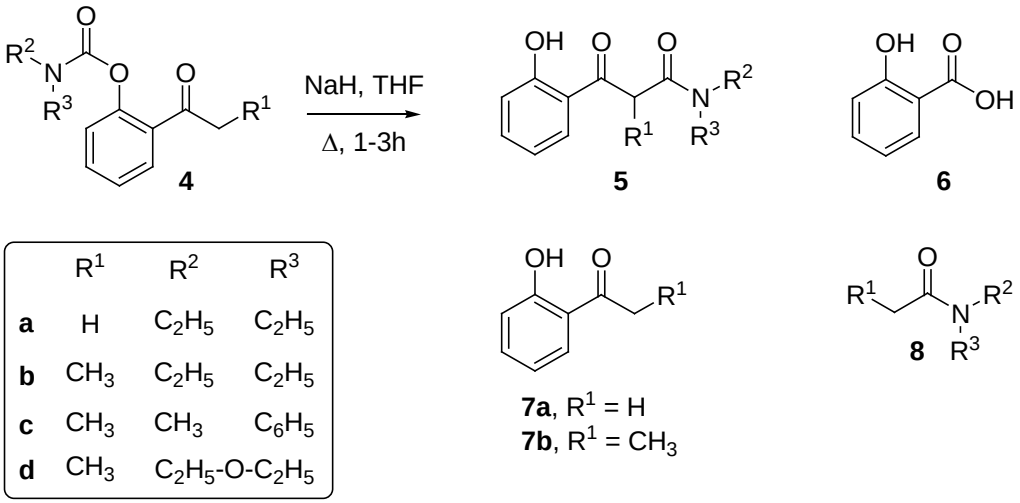


Scheme 1. Snieckus's carbamoyl variant of the Baker-Venkataraman rearrangement.

Recently we sought to develop a new series of asymmetric reactions by expanding the substrate scope of the Baker-Venkataraman reaction along with its mechanistically related *O*→*C* aryl migration counterpart, the Truce-Smiles reaction.[3] During the course of preliminary development work, attention turned to Snieckus's carbamoyl Baker-Venkataraman variant as a way of exploring

an asymmetric variant, but utilising a series of substrates where the 1,3-dicarbonyl products (see **2**, Scheme 1) are less prone to enolisation, and thus less likely to racemise any induced asymmetry. In the event, during the initial stages of screening suitable reaction conditions for the Baker-Venkataraman rearrangement, a new cascade reaction was identified which saw an alkyl group apparently migrate from the ketone motif of the starting material to the carbamoyl group of the same molecule; this communication describes the nature of the proposed Baker-Venkataraman *retro*-Claisen cascade mechanism that gives rise to the observed products.

Whilst initially attempting to develop suitable rearrangement conditions on achiral substrates, carbamates, such as **4** (Scheme 2), were studied and familiarisation of the reaction began by employing Snieckus's conditions[2a] on substrate **4a**. Unfortunately, in our hands, this reaction gave a mixture of products which contained, amongst other things, the desired rearrangement product **5a**, along with significant quantities of salicylic acid (**6**). Repeating the reaction with carbamoyl substrates **4b-d** again resulted in a mixture of the desired rearrangement products **5b-d** and salicylic acid (**6**). However, on these repeat runs the unwanted hydrolysis products (**7a,b**) as well as the amides (**8b-d**) were also obtained (Scheme 2). These results were in contrast to those of Snieckus where the 1,3-dicarbonyl products **2** were obtained in good to excellent yields (Scheme 1, 78-97%).[2a] Conversely, in our hands, when using strictly anhydrous conditions, results comparable to those of Snieckus (Table 1 column (I)) were eventually successful. Based on these conflicting, yet intriguing results, attempts were made to study the "wet" reaction to see if the unexpected process could be repeated and made more general through establishing some preliminary substrate scope and limitations.



	R^1	R^2	R^3
a	H	C_2H_5	C_2H_5
b	CH_3	C_2H_5	C_2H_5
c	CH_3	CH_3	C_6H_5
d	CH_3	C_2H_5-O-C_2H_5	

Scheme 2. Initial attempts at the carbamoyl Baker-Venkataraman rearrangement.

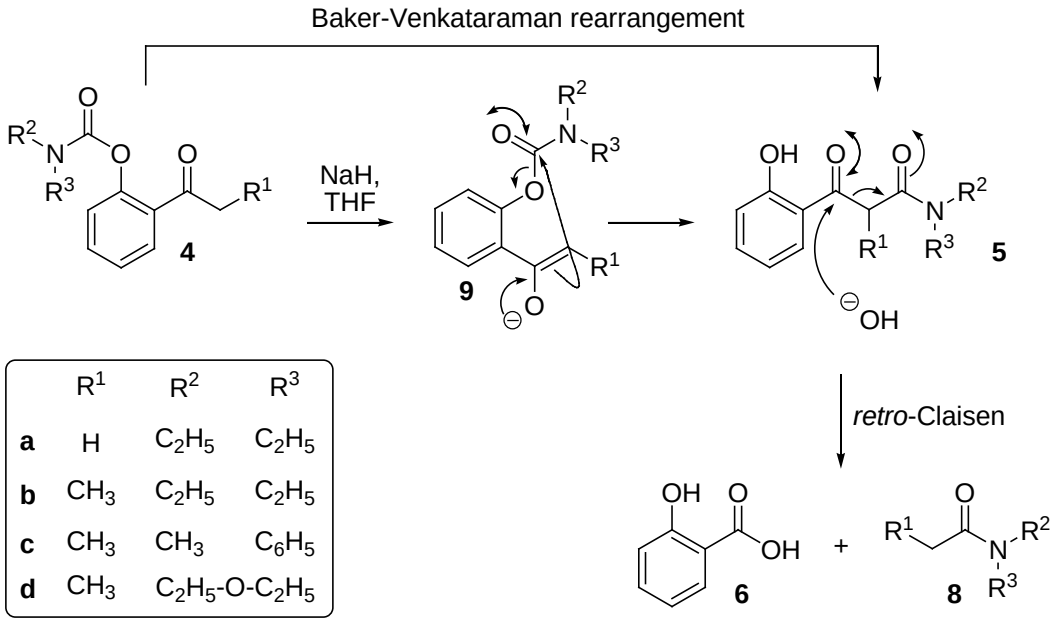
Upon examining the reaction in more detail, it was observed (Table 1, column II) that heating the substrates (**4a-d**) in tetrahydrofuran (0.2 M) at reflux, with sodium hydride (2.5 equivalents), for an extended period of 24 hours, offered a more reliable way of obtaining a mixture of salicylic acid (**6**), the hydrolysis products (**7**), and amides (**8**), but with none of the associated rearranged products (**5**). Presumably, when the longer reaction time was employed (i.e. 24 h rather than 1-3 h), the Baker-Venkataraman rearranged products (**5a-d**) do form *in situ* but subsequently undergo a second reaction, reminiscent of an intramolecular *retro*-Claisen condensation, to give salicylic acid (**6**) and amides **8a-d** (Scheme 3).

Table 1. Substrates undergoing the carbamoyl Baker-Venkataraman rearrangement (I) and the carbamoyl Baker-Venkataraman *retro*-Claisen cascade (II).

			(I) "anhydrous"	(II) "wet"		
Entry	R^1-R^3	**4**[a] (%)[b]	**5** (%)[b]	**6** (%)[b]	**7** (%)	**8** (%)[b]
1	**a**	27	74	45	-[d]	trace[e]
2	**b**	32	N.A.[c]	50	-[d]	trace[e]
3	**c**	76	48-92[f]	42	-[d]	41
4	**d**	94	N.A.[c]	27	-[d]	trace[e]

Reaction conditions: "anhydrous": sodium hydride (2.5 eq.), reflux, 1-3 hours, anhydrous THF (0.2M), 4Å molecular sieves; "wet": sodium hydride (2.5 eq.), reflux, 24 hours, THF. [a] Prepared in one-step from the corresponding phenol (1.0 eq.), carbamoyl chloride (1.5 eq.), triethylamine (1.5 eq.) and 4-dimethylaminopyridine (0.1 eq.) in CH_2Cl_2 (0.1M) at 0 °C; [b] Isolated yields; [c] N.A. = not attempted; [d] Product not isolated; [e] In these cases the trace product observed may be the result of having lost the amide product during reaction work-up, not necessarily that it was not formed during the reaction; [f] On certain occasions this compound was observed to cyclise to give a mixture of products, see Scheme 4.

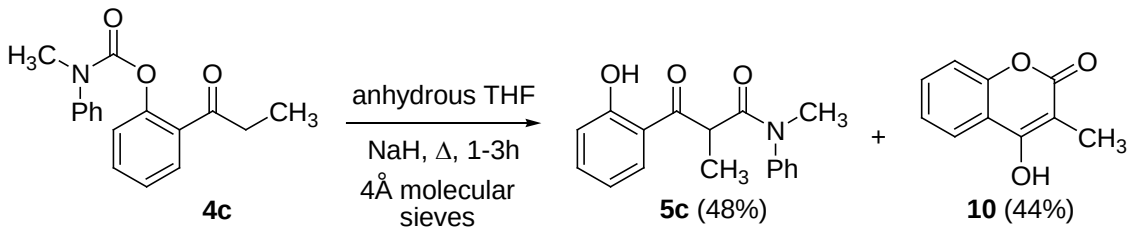
When using substrates **4a,b,d** the reaction did not yield any significant quantities of isolated amide products (**8a,b,d**), whilst carbamate **4c** gave amide **8c** in 41% yield. These results do not necessarily mean that amides **8a,b,d** did not form during the reaction, simply that they are too volatile or water soluble, to be isolated after aqueous workup. Nevertheless, upon reflection of the proposed mechanism (Scheme 3), evidence that the amide must have formed at the same conversion as salicylic acid during the reaction is provided by the formation, isolation and characterisation of salicylic acid itself (**6**, 27-50%) in each of those reactions (see Scheme 2 and Table 1 (column II)).



Scheme 3. Proposed mechanism of the Baker-Venkataraman *retro*-Claisen cascade.

Scheme 3 shows that under the conditions employed, a proton would be abstracted by sodium hydride (or sodium hydroxide formed *in situ*) to form enolate **9** which in turn attacks the carbonyl of the carbamate group to form a six-membered cyclic intermediate which would collapse to generate the Baker-Venkataraman rearrangment product **5**. Nucleophilic addition of trace hydroxide could then attack the rearranged product at the more reactive ketone carbonyl group and consequently a *retro*-Claisen carbon-carbon bond cleavage would occur to yield salicylic acid (**6**) and the amide derivatives (**8**). A process which would see the overall transformation (**4**→**8**) as the apparent migration of $–CH_2R^1$ from the ketone in the starting material to the carbamoyl group.

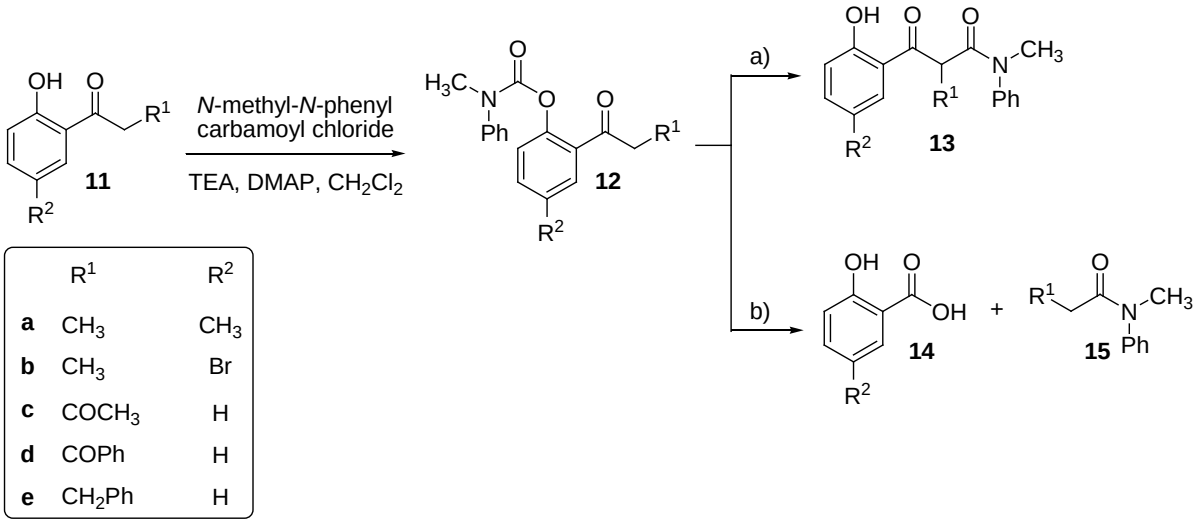
As expected,[2a] when the carbamoyl Baker-Venkataraman rearrangement substrate **4c** was heated at reflux for the shorter time of 1-3 hours, in anhydrous tetrahydrofuran containing sodium hydride and 4Å molecular sieves, only the rearrangement product **5c** (48%) was obtained (Scheme 4, in addition to product **10** (44%), which is the result of the phenolic –OH in **5c** intramolecularly attacking the amide carbonyl), but no *retro*-Claisen products (**6** and **8c**) were observed.



Scheme 4. The products obtained under anhydrous conditions.

Further evidence for the proposed mechanism (Scheme 3) was obtained when the reaction was performed with **4c**, in a THF:MeOH solution and the corresponding methyl salicylate was obtained, rather than the usual salicylic acid obtained when water is present.

In order to demonstrate the generality of this Baker-Venkataraman *retro*-Claisen cascade, five more 2'-hydroxypropiophenone derivatives **11a-e** were acylated successfully with *N*-methyl-*N*-phenylcarbamoyl chloride to give the corresponding carbamoyl-based Baker-Venkataraman rearrangement substrates **12a-e**, compounds from which it is expected that non-volatile, non-water-soluble, and isolable amide products would form. Repeatedly, it was found that four of the carbamoyl substrates attempted (**12a,b,d,e**) underwent the Baker-Venkataraman *retro*-Claisen cascade to give the corresponding salicylic acid and amide derivatives (**14a,b,d,e** and **15a,b,d,e** respectively) when subjected to the "wet" reaction conditions, Scheme 5 and Table 2, column II.



	R^1	R^2
a	CH_3	CH_3
b	CH_3	Br
c	$COCH_3$	H
d	COPh	H
e	CH_2Ph	H

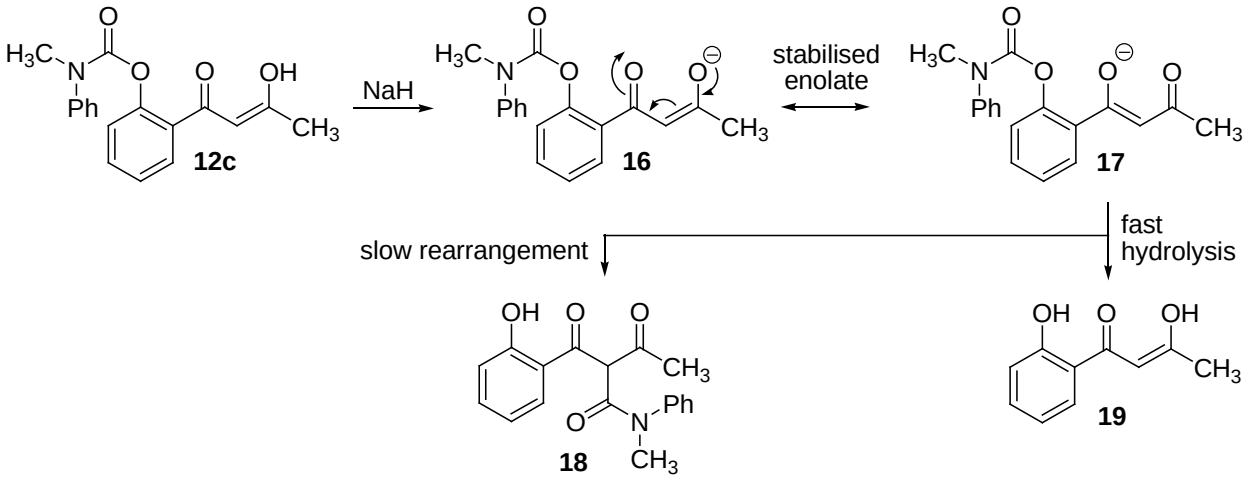
Scheme 5. *Reaction conditions*: a) "anhydrous" conditions: sodium hydride (2.5 eq.), reflux, 1-3 hours, anhydrous THF (0.2M), 4Å molecular sieves; b) "wet" conditions: sodium hydride (2.5 eq.), reflux, 24 hours, THF. TEA = triethylamine; DMAP = 4-dimethylaminopyridine.

Table 2. Carbamoyl Baker-Venkataraman rearrangement substrates undergoing the Baker-Venkataraman rearrangement only (I), and a Baker-Venkataraman *retro*-Claisen cascade (II).

			(I) "anhydrous"	(II) "wet"	
Entry	R^1-R^2	**12** (%)[a,b]	**13** (%)[a]	**14** (%)[a, d]	**15** (%)[a, d]
1	**a**	63	22	25	85
2	**b**	96	N.A.[c]	43	60
3	**c**	50	N.A.[c]	-[d]	-[d]
4	**d**	91	0[f]	0	0[e]
5	**e**	99	58	42	42

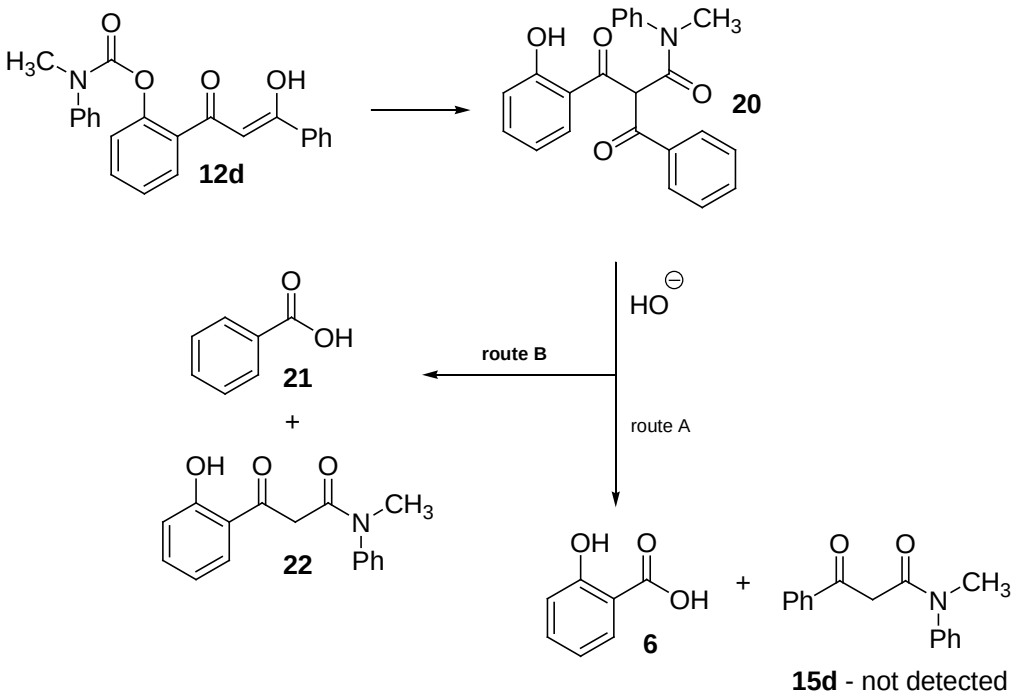
Reaction conditions: "anhydrous": sodium hydride (2.5 eq.), reflux, 1-3 hours, anhydrous THF (0.2M), 4Å molecular sieves; "wet": sodium hydride (2.5 eq.), reflux, 24 hours, THF. [a] Isolated yields; [b] For the synthesis of **12** see Table 1; [c] N.A. = not attempted; [d] In all cases the remaining yield is made up of the corresponding hydrolysis products (**11**). [e] In the case of substrate **12d**, a different rearrangement product **22** was formed instead of the expected amide **15d** (for a detailed explanation see Scheme 7). [f] The rearrangement product **22** was isolated in 33% yield.

As can be seen from Table 2 (column II), only substrate **12c** (R^1 = $COCH_3$, R^2 = H) failed to undergo the Baker-Venkataraman *retro*-Claisen cascade. Instead the hydrolysed product **11c** was detected as the sole product. This result can be rationalised by the fact that the 1,3-dicarbonyl system in **12c** can form a stabilised enolate (as shown in Scheme 6, **16**↔**17**), therefore, although it might undergo a slow rearrangement to **18** it would no doubt suffer from a faster hydrolysis step to **19** in the conditions used with residual water, Scheme 6.



Scheme 6. Failure of **12c** to undergo the Baker-Venkataraman *retro*-Claisen cascade.

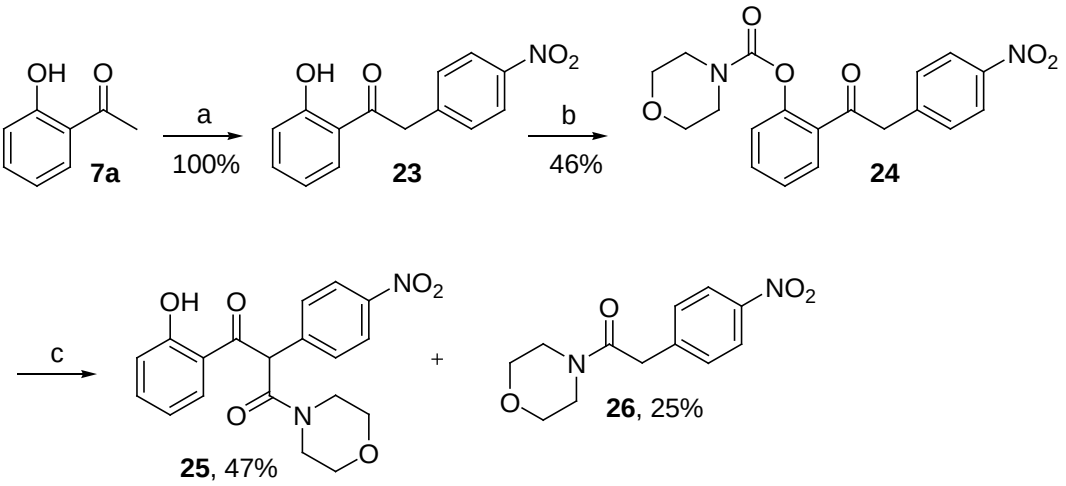
In the case of substrate **12d**, a different rearrangement product was formed (see **22**, Scheme 7) instead of the expected amide **15d**. The rationale for the formation of **22** is that the hydroxide ion may attack the arylketone via route A or route B. Based upon the structure of the isolated product, the hydroxide attacks more electrophilic benzoyl carbon (route B) during the *retro*-Claisen step to give product **22** (33%) and benzoic acid (**21**). This result was observed only in "anhydrous" conditions giving a 33% yield of **22**, whereas in our normal "wet" conditions only 8% of **22** was detected, the reduced yield presumably due to a faster competing hydrolysis of **12d**, which gave **11d** in 92% yield; a similar level of reactivity was seen with **12c**.



Scheme 7. Proposed mechanism for the formation of compound **22**.

Whilst compound **15e** (Table 2) is a known chymotrypsin inhibitor,[4] it was believed that a worthy test of the method would be to attempt to synthesise **26** (Scheme 8), a known alanyl aminopeptidase inhibitor,[5] that would require a multistep protocol. In the event, 2'-hydroxyacetophenone (**7a**) was subject to a Truce-Smiles rearrangement,[3c] which resulted in the α-arylated product **23** in quantitative yield, after which, carbamoylation gave the Baker-Venkataraman precursor **24** (46%). Subjecting **24** to the standard conditions (2.5 eq. NaH, "wet" THF 0.1M, reflux, 24 h) then afforded a separable mixture of the Baker-Venkataraman rearranged product **25** (47%) and the desired *retro*-

Claisen cascade product **26** (25%), the low yield presumably due to incomplete *retro*-Claisen of **25** during the reaction.



Scheme 8. Synthesis of a known alanyl aminopeptidase inhibitor (**26**). *Reaction conditions*: a) **7a** (1 eq.), 1-fluoro-4-nitrobenzene (1 eq.), K_2CO_3 (2.5 eq.), DMSO (0.1M), 60 °C, 24 hours; b) **23** (1 eq.), 4-morpholinecarbonyl chloride (1.5 eq.), triethylamine (1.5 eq.) and 4-dimethylaminopyridine (0.1 eq.), dichloromethane (0.1 M), room temp., 16 hours; c) **24** (1 eq.), sodium hydride (2.5 eq.), reagent grade tetrahydrofuran (0.2 M), reflux, 24 hours.

Conclusion

In conclusion, it has been shown that the carbamoyl variant of the Baker-Venkataraman rearrangement gives *retro*-Claisen cascade products if the anhydrous conditions of the reaction are not carefully controlled. Rather than the expected products resulting from carbamate hydrolysis that are obtained with the analogous ester and carbonate compounds,[6] when residual water is present in the carbamoyl variant, a Baker-Venkataraman *retro*-Claisen cascade takes place giving amide products in which an alkyl group apparently migrates from the ketone motif of the starting material to the carbamoyl group of the same molecule.

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References

(1) Ameen. D.; Snape, T. J. *Synthesis*, **2014**, *In Press (Accepted).*

(2) (a) Kalinin, A. V.; da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995(b) Kalinin, A. V.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4999(c) Chauder, B. A.; Kalinin, A. V.; Taylor, N. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **1999**, *38*, 1435.
(3) (a) Ameen, D.; Snape, T. J. *Eur. J. Org. Chem.* **2014**, 1925(b) Snape, T. J. *Synlett* **2008**, 2689(c) Snape, T. J. *Chem. Soc. Rev.* **2008**, *37*, 2452.
(4) Baker, B. R.; Hurlbut, J. A. *J. Med. Chem.* **1967**, *10*, 1129.
(5) Ansorge, S.; Bank, U.; Nordhoff, K.; Striggow, F.; Taeger, M. Novel alanyl-amino peptidase inhibitors for functionally influencing different cells and treating immunological, inflammatory, neuronal, and other diseases, WO 2005037257 A2, **2005**.
(6) Ameen, D. M. H., Ph.D. Thesis, University of Central Lancashire **2014**.