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Reaction of Arynes with Vinylogous Amides: Nucleophilic Addition to the *ortho*-Quinodimethide Intermediate

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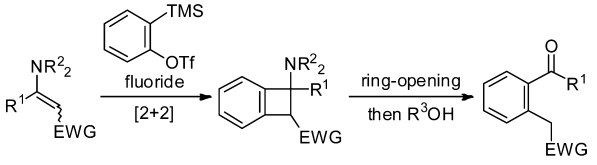
ABSTRACT



The reaction of arynes with vinylogous amides containing no free N−H bonds proceeds in a [2 + 2] cycloaddition fashion at ambient temperature. The electronic properties of the vinylogous amides allow for the cycloadducts undergoing a facile ring-opening process, leading to electronically biased *ortho*-quinodimethide intermediates. Subsequent nucleophilic addition with alcohols affords 2-substituted benzaldehydes or ketones.

In the past decade, aryne chemistry has become an emerging area in organic synthesis.[1] Among the hot topics, those involving nucleophilic addition and pericyclic reactions have been heavily studied, many of which exhibit considerable theoretical value and/or complement conventional approaches in a synthetic point of view.

Since aryne is electrophilic, efforts to seek the nucleophilic partner are continuing. Recently, several marked reports have disclosed that enamides can nucleophilically react with arynes. Depending on the structure of the enamides, [2 + 2] cycloaddition,[2] [3 + 2] annulation,[3] [4 + 2] annulation,[4] as well as β-arylation[5] can take place. However, closely related vinylogous amides (**1**, Scheme 1) have not been studied much in aryne chemistry.[6] Vinylogous amides have been traditionally considered a subtype of enamides, but their C=C double bonds are more electronically biased. We considered that the push−pull nature of this double bond should feature an easier [2 + 2] cycloaddition with arynes (for vinylogous amides without free N−H bonds, Scheme 1, first step). Thus, unlike typical enamides, whose [2 + 2] cycloaddition requires 110 °C,[2a,b] vinylogous amides may react with arynes under much milder conditions. Moreover, it has been known that the stability of the [2 + 2] cycloadduct **3** is also heavily dependent upon its electronic properties: the more electron-rich the nitrogen, the easier it will undergo a ring-opening process to afford an *ortho*-quinodimethide (*o*QDM) (Scheme 1, second step).[7,8] Mechanistically, this can be explained as the ring-opening for the vinylogous amide cycloadducts, compared to that for the typical enamide cycloadducts, deviates from a strict retro-4π

(1) For recent reviews: (a) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (b) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (c) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725. (d) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (e) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116.

(2) (a) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3666. (b) Ma, Z.-X.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 2742. (c) Blackburn, T.; Ramtohul, Y. K. *Synlett* **2008**, 1159.

(3) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.

(4) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2012**, 8105. See also refs 2c and 3.

(5) The β-arylation was reported in ref 2c with a single example. It was not thoroughly studied.

(6) There is a report where aryne reacts with vinylogous amides containing free NH bonds in a β-arylation fashion. See: Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029.

(7) Oppolzer, W. *Synthesis* **1978**, 793.

(8) For reviews of *o*QDMs, see: (a) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199. (b) Collier, S. J.; Storr, R. C. Heterocyclic *ortho*-Quinodimethanes. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Elsevier Science: Oxford, UK, 1998; Vol. 10, pp 25−48. (c) McCullough, J. J. *Acc. Chem. Res.* **1980**, *13*, 270. (d) Fishwick, C. W. G.; Jones, D. W. *ortho*-Quinonoid Compounds. In *The Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, UK, 1988; Vol. 1, pp 403−453.

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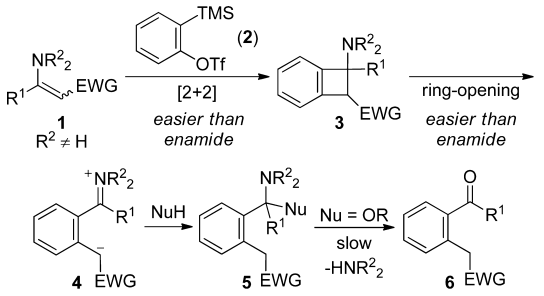
Scheme 1. Proposed Reaction Mechanism and Outcome



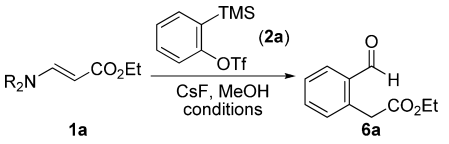
electrocyclic process to a lone-pair-assisted cleavage of the $C(sp^3)-C(sp^3)$ bond of the four-membered ring.[9] Thus the resultant *o*QDM exists rather as an iminium inner salt **4**.

This speaks for two things. First, the ring-opening process for the vinylogous amide cycloadducts ($R^2 \neq H$ or EWG) should be much more facile and might occur at ambient temperature (compared to 110 °C for that of enamides[2a,b]). Second, the reactivity of **4** can be exploited, for example, in a nucleophilic addition reaction leading to product **5**, thereby featuring an overall *ortho*-difunctionalization of arynes. This concept has been previously attempted on *ortho*-quinomethide (*o*QM) intermediates generated from aryne cycloaddition/ring-opening with DMF,[10] but the scope was limited and has not yet been applied to *o*QDMs.

One should notice that the direct reaction of this external nucleophile with arynes must be minimized. Thus, in addition to the reported nucleophiles used in the DMF system,[10] we envisioned that simple aliphatic alcohols appear a general, ideal candidate here, thanks to its low reactivity with arynes.[11] Thus, **4** may be readily quenched by an alcohol, leading to an aminal **5**, which should eventually afford a carbonyl compound **6**. Intermediate **5** is expected to be stable enough and release the highly "arynophilic" amine only slowly so that its reactivity with arynes was also minimized.

As such, substrate **1a** was first studied against different reaction conditions (Table 1). Despite a background reaction presumably caused by moisture (entries 1 and 2), addition of 1.5 equiv of MeOH significantly improved the yield (entry 3). Too much MeOH proved detrimental (entry 4). The best amine moiety was dibenzylamine or diisopropylamine (entries 3 and 5), but a morpholino group also afforded acceptable result (entry 6). Pyrrolidinyl was not a group of choice (entry 7). For subsequent studies,

Table 1. Reaction Optimization[a]



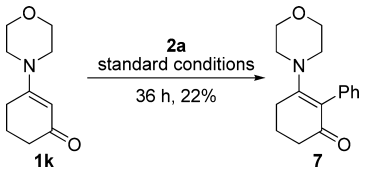
entry	NR_2 (**1a**)	MeOH/ equiv	conditions	yield[b] (%)
1	NBn_2 (**1a-Bn**)	0	MeCN, rt, 36 h	39
2	NBn_2	0	THF, 70 °C, 36 h	28
3	NBn_2	1.5	MeCN, rt, 24 h	83
4	NBn_2	3	MeCN, rt, 36 h	52
5	N^iPr_2 (**1a-Pr**)	1.5	MeCN, rt, 24 h	82
6	morpholino (**1a-mor**)	1.5	MeCN, rt, 24 h	66
7	pyrrolidinyl (**1a-pyr**)	1.5	MeCN, rt, 24 h	23

[a] All reactions were carried out on 0.3 mmol of **1a** with 1.5 equiv of **2a** and 3 equiv of CsF in 4.5 mL of solvent. [b] Isolated yield.

we elected the morpholino group due to its broader compatibility than the dibenzylamino group.[12]

With these conditions in hand, we tested the scope and limitation of this chemistry. The reaction tolerated several symmetrical or unsymmetrical arynes (entries 1–3, Table 2). Aryne **2c** afforded **6c** as the only isolable isomer (entry 2). The scope of vinylogous amides was reasonable. Of note was that those substrates with aliphatic R^1 groups gave inferior yields (compare entries 4 and 5, entries 10 and 11), presumably due to the competing deprotonation or internal proton transfer process at the stage of **4**.[13] The electronic properties of R^1 proved fairly irrelevant (entries 6–8). The electron-withdrawing group (EWG) could successfully cover ester (entries 1–8), tertiary amide (entry 9), ketone (entries 10 and 11), and cyano (entry 12) groups. Substrates with an EWG being secondary amides (with a free N–H bond) did not work well (not shown).

Scheme 2. Cyclic Substrate



Exceptions exist. For example, vinylogous amides derived from acetylenedicarboxylates failed to afford product **6** (not shown).[14] The cyclic substrate **1k** led to a smooth β-arylation event in a low yield (Scheme 2).

As stated before, a reasonably high yield of **6** must mean a slow release of the amine from adduct **5**, so that the side reaction of amine with aryne is suppressed. However, given

(9) This is suggested by a reviewer, and we thank him/her for this comment.

(10) (a) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638. (b) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956. (c) Yoshioka, E.; Miyabe, H. *Tetrahedron* **2012**, *68*, 179. (d) Yoshioka, E.; Tanaka, H.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2013**, *15*, 3938.

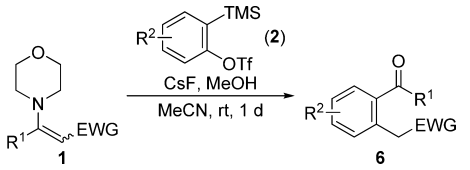
(11) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.

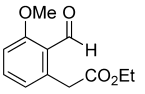
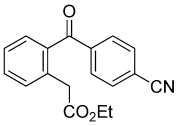
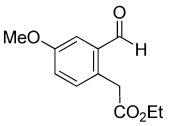
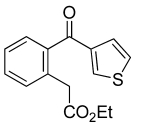
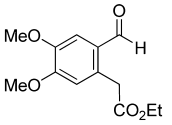
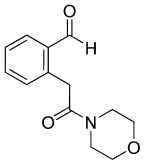
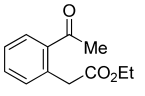
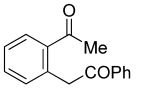
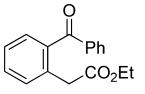
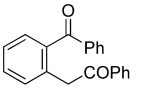
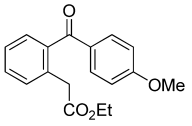
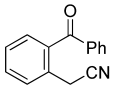
(12) For unclear reasons, most morpholino-substituted substrates with $R^1 \neq H$ (**1**, cf. Scheme 1) gave much better yields than those Bn_2N-substituted counterparts. This would also mean that the yields reported in entries 1–3 in Table 2 may be underestimated.

(13) Unforunately, to date, we have been unsuccessful in preparing the substrate with R^1 being a *tert*-butyl group.

(14) The identity of the product is under investigation and will be disclosed in due course.

Table 2. Reaction Scope[a]



entry	1 (R^1, EWG)	2 (R^2)	product	yield[b] (%)	entry	1 (R^1, EWG)	2 (R^2)	product	yield[b] (%)
1	**1a-mor**	**2b** R^2 = 3-OMe	 **6b**	69	7	**1e** R^1 = 4-(NC)C_6H_4 EWG = CO_2Et	**2a**	 **6h**	50
2	**1a-mor**	**2c** R^2 = 4-OMe	 **6c**	50	8	**1f** R^1 = 3-thiophenyl EWG = CO_2Et	**2a**	 **6i**	83
3	**1a-mor**	**2d** R^2 = 4.5-$(OMe)_2$	 **6d**	60	9	**1g** R^1 = H EWG = CO(morpholino)	**2a**	 **6j**	57
4	**1b** R^1 = Me EWG = CO_2Et	**2a**	 **6e**	31	10	**1h** R^1 = Me EWG = COPh	**2a**	 **6k**	49[c]
5	**1c** R^1 = Ph EWG = CO_2Et	**2a**	 **6f**	81[c]	11	**1i** R^1 = Ph EWG = COPh	**2a**	 **6l**	71
6	**1d** R^1 = 4-(MeO)C_6H_4 EWG = CO_2Et	**2a**	 **6g**	55	12	**1j** R^1 = Ph EWG = CN	**2a**	 **6m**	45

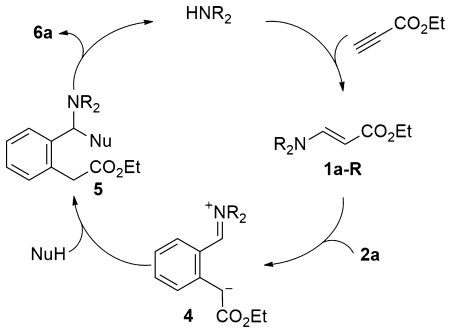
[a] Reactions conditions: **1** (0.3 mmol), **2** (0.45 mmol), CsF (0.9 mmol), and MeOH (0.45 mmol) in 4.5 mL of MeCN. Reactions may not be individually optimized. [b] Isolated yield. [c] Reaction took 12 h.

the low concentration of the aryne, we considered that in the presence of a second strong electrophile, the released amine would have less chance to react with arynes. Since a vinylogous amide can be generated in situ from a propiolate and an amine, we reasoned that a propiolate–amine–aryne system may constitute a three-component variant of this chemistry, where amine may be used in catalytic amount (Scheme 3).

Ideally, in this scenario, amine would first react with propiolate to form the vinylogous amide **1**, which should subsequently react with aryne, as described in Scheme 1, to generate **4**. Nucleophilic addition then affords **5**, which slowly releases the desired product **6** while regenerating the amine. We tested this possibility (Table 3) using a model reaction containing ethyl propiolate, benzyne precursor **2a**, and an alcohol as the nucleophile in the presence of a secondary amine in catalytic quantity. We incorporated 2 equiv of propiolate to prevent the amine from reacting with benzyne and used **2a** as the limiting reagent. Although a synthetically useful yield has not been realized, the concept proved amendable. Up to 4 turnovers of amine could be

(15) Increasing the quantity of amine did not significantly improve the overall yield. For additional results, see the Supporting Information.

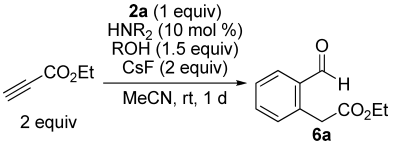
Scheme 3. Proposed Catalytic Variant



realized.[15] The nature of alcohol was not critical, as MeOH, EtOH, or ^{i}PrOH afforded the same yield and turnover. Only tertiary alcohols such as ^{t}BuOH were problematic, likely due to its lowered nucleophilicity. Currently, we tend to believe that the low turnover number might result from the undesirable kinetics of some steps in this catalytic cycle,[16] as well as the loss of the amine for side reactions.

In summary, our preliminary results have demonstrated that vinylogous amides react with arynes in a [2 + 2] cycloaddition/ring-opening fashion to furnish an electronically biased *o*QDM intermediate (rather as an iminium inner salt). The electronic properties of vinylogous amides not only allow for this process taking place at ambient temperature but also render this *o*QDM intermediate the opportunity for being trapped by a nucleophile to achieve *ortho*-difunctionalization of arynes.[17] Although the synthetic utilities of the *o*QDM intermediate have to be further exploited,[18,19] we believe that this preliminary study complements the aryne reactivity with enamides and supports that fine-tuning of a nucleophile may result in significantly altered mechanism, reaction conditions, and final product in aryne chemistry. Further studies to expand the scope are underway.

Table 3. Catalytic Protocol[a]



entry	HNR_2	ROH	yield[b] (%)
1	$HNBn_2$	MeOH	26
2	morpholine	MeOH	38
3	TMP[c]	MeOH	trace
4	$HN^{i}Pr_2$	MeOH	40
5	$HN^{i}Pr_2$	EtOH	36
6	$HN^{i}Pr_2$	^{i}PrOH	40
7	$HN^{i}Pr_2$	^{t}BuOH	trace

[a] All reactions were carried out on 0.3 mmol of **2a** in 4.5 mL of MeCN. Amine and propiolate were mixed first in solvent, and all other reagents were added after 1 h. [b] Isolated yield. [c] TMP = 2,2,6,6-tetramethylpiperidine.

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Supporting Information Available. Additional results for the cataytic protocol, experimental details, and characterization of the products, including full ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) The narrow scope for the catalytic protocol also comes from the undesirable kinetics of the first step. For example, many electron-poor alkynes react with secondary amines only at elevated temperature, which is not tolerated for the subsequent reaction with arynes.

(17) A related process offering a similar outcome but a completely different mechanism is the aryne reaction with β-dicarbonyl compounds. See: (a) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (b) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292. Since some vinylogous amides can be prepared from β-dicarbonyl compounds, some of our products (e.g., **6e**, **6f**, **6l**) are accessible that way. However, (i) such an event has not been known to deliver products with aldehyde moieties (e.g., **6a**) or been compatible with β-ketoamides (e.g., **6j**); (ii) the regioselectivity with unsymmetrical β-diketones (e.g., for **6k**) has not been resolved; (iii) vinylogous amides can also be prepared from other substrates (e.g., substituted propiolates), and therefore, our reaction has broader product scope.

(18) Our preliminary studies to react the *o*QDM intermediate with dienophiles in an *intermolecular* [4 + 2] cycloaddition fashion have been unsuccessful.

(19) Our preliminary studies to react the iminium functionality of **4** with other possible nucleophiles, including $NaBH_4$ and aryl boronic acid, have also been unsuccessful.

The authors declare no competing financial interest.