ORGANIC LETTERS

2007
Vol. 9, No. 6
1029−1032

Direct C-Arylation of β-Enamino Esters and Ketones with Arynes

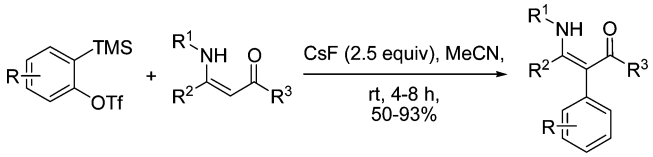
Yeeman K. Ramtohul* and Anik Chartrand

Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, Merck Frosst Canada & Co., Inc., P.O. Box 1005, 16711 Trans Canada Highway, Kirkland, Quebec, Canada H9H 3L1

yeeman_ramtohul@merck.com

Received December 18, 2006

ABSTRACT



An efficient, mild, and general method for the C-arylation of β-enamino esters and ketones with arynes has been developed. This methodology provides a facile and direct access to a variety of substituted aromatic β-enamino compounds in moderate to excellent yield.

With the development of a mild and general method for the generation of arynes from *ortho*-silyl aryltriflates and a fluoride anion,[1] the use of aryne has seen a growing interest in the field of organic synthesis.[2,3] Because of its electrophilicity, a wide variety of anionic and uncharged nucleophiles add readily to arynes which represent a direct approach to access substituted arenes.[2] In most cases, when an electrophile is tethered to the nucleophile, the initially formed zwitterion (Figure 1) undergoes a subsequent intramolecular

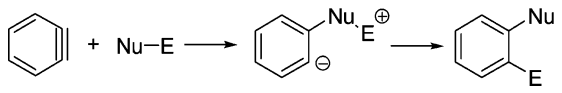


Figure 1. Insertion of benzyne into a nucleophile−electrophile σ-bond (Nu−E).

reaction with the electrophile leading to the formal insertion of the aryne into the Nu−E σ-bond.

Typical examples for the insertion of arynes into a heteroatom−hydrogen bond include amines, sulfonamides, carbamates, phenols, and carboxylic acids.[4] However, when active methylene compounds such as β-keto esters,[5] malonate esters,[6] and α-cyanocarbonyl compounds[7] are used as the nucleophile, the net result is insertion of the aryne between the α-methylene and the carbonyl group to generate *ortho*-disubstituted arenes.

Because amino groups are known to react with benzyne,[4,8] we attempted N-arylation of β-enamino esters **2a** with the benzyne precursor *ortho*-silyl aryltriflate **1** in the presence of CsF in CH_3CN at 80 °C (Table 1, entry 1). Interestingly,

(1) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211−1214.

(2) For a review on the nucleophilic coupling with arynes, see: Kessar, S. V. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 483−515.

(3) (a) For the application of arynes in total synthesis, see: Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752−11753. (b) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436−2440.

(4) Liu, Z. J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198−3209 and references therein.

(5) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340−5341.

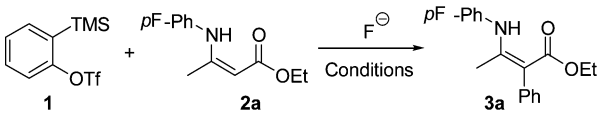
(6) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292−3294.

(7) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729−6731.

(8) (a) Liu, Z. J.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673−4675. (b) Liu, Z. J.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739−3741. (c) Liu, Z. J.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112−13113. (d) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247−3249. (e) Yoshida, H.; Minabe, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 34540−3456. (f) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040−11041.

10.1021/ol063057k CCC: $37.00 © 2007 American Chemical Society
Published on Web 02/20/2007

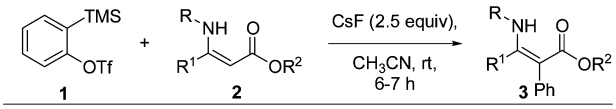
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	$F^{\ominus}$ source (equiv)	triflate (equiv)	temp (°C)	time (h)	yield (%)[b]
1	CH_3CN	CsF (2.5)	1.25	80	2	71
2	CH_3CN	CsF (2.5)	1.25	60	4	86
3	CH_3CN	CsF (2.5)	1.25	50	5	84
4	CH_3CN	CsF (2.5)	1.25	40	6	82
5	CH_3CN	CsF (2.5)	1.25	rt	7	87
6	CH_3CN	CsF (1.5)	1.25	rt	8	77
7	CH_3CN	CsF (1.1)	1.25	rt	9	75
8	THF	TBAF (2.5)	1.25	rt	2	64
9	THF	KF/18-C-6 (1.5)	1.5	rt	3	26

[a] Reaction conditions: 0.4 mmol of the β-enamino ester **2a** in 0.2 M solvent in a sealed vial. [b] Isolated yield.

Table 2. C-Arylation of β-Enamino Esters with Benzyne[a]



Entry	β-Enamino Ester		Product	Yield (%)[b]
1	R = *p*F-Ph	**2a**	**3a**	87[c]
2	R = Ph	**2b**	**3b**	87[c]
3	R = *n*-Bu	**2c**	**3c**	50[c]
4	R = *i*-Pr	**2d**	**3d**	58[c]
5	R^1 = Me, R^2 = OMe	**2e**	**3e**	72[c]
6	R^1 = *p*CF_3-Ph, R^2 = OMe	**2f**	**3f**	84
7	R^1 = *p*F-Ph, R^2 = OEt	**2g**	**3g**	91[c]
8	R^1 =  , R^2 = OEt	**2h**	**3h**	71

[a] Reaction conditions: 1.25 equiv of *ortho*-silyl aryltriflate **1**, 1 equiv (0.4 mmol) of the β-enamino ester **2**, 2.5 equiv of CsF, 0.2 M CH_3CN in a sealed vial at room temperature. [b] Isolated yield. [c] Configuration of the double bond was determined by NOE.

no N-arylation product was isolated and instead reaction occurred at the α-carbon to generate the C-arylation product **3a** in 71% yield. Moreover, although an ester group is present, no insertion of the benzyne into the α-carbon and carbonyl σ-bond was observed as is the case with β-keto esters,[5] malonate esters,[6] and α-cyanocarbonyl compounds.[7] β-Enamino esters are interesting motifs as they can be reduced asymmetrically and transformed into chiral β-amino acids.[9] To the best of our knowledge, no direct intermolecular arylation of β-enamino esters involving arynes has been reported, although some examples of arylation employing transition-metal and radical-mediated reactions have been published.[10] Herein, we report an efficient and facile intermolecular C-arylation of β-enamino esters and ketones with arynes under mild conditions.

We first examined the effect of temperature on the arylation of the β-enamino ester **2a** and found that a lower temperature is more favorable (Table 1, entries 2−5), although a longer reaction time is needed. However, using less CsF (entries 6 and 7) lowered the yield slightly and using other reported sources of fluoride for generating aryne such as TBAF[1] and KF/18-Crown-66 had a deleterious effect on the yield (entries 8 and 9). Because TBAF and KF/18-Crown-6 generate benzyne much faster due to the higher concentration of fluoride anions, it seems that the slow formation of aryne under the heterogeneous condition of CsF/CH_3CN at room temperature is more conducive for this reaction. With the optimal conditions set, we began investigating the substrate scope with a variety of β-enamino esters **2a**−**h**. As shown in Table 2, aromatic and aliphatic substitution on the nitrogen are tolerated in **2a**−**d**. However, when a γ-ester group is present in **2c** and **2d**, the yield is moderate presumably due to the decreased nucleophilicity of the enamine. Interestingly, a free amino group is well tolerated in **2e**−**h** and no N-arylation product was observed. In addition, a furan derivative, which is known to undergo Diels−Alder cycloaddition with benzyne,[11] is tolerated as well (entry 8), affording mainly the C-arylation product **3h** in good yield. It should be noted that the configuration of the double bond is retained in the reaction and that only the *Z*-isomer was produced as determined by an NOE experiment for representative compounds.

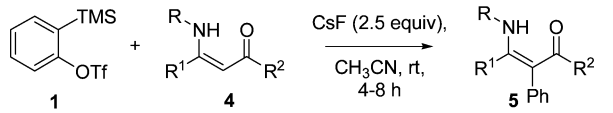
With the encouraging results obtained, our next approach was to extend the substrate scope to include β-enamino ketones. As illustrated in Table 3, β-enamino ketones **4a**−**j** work as well affording moderate to high yields of the corresponding arylated β-enamino ketones **5a**−**j**. Functionalities such as olefin **4c** and alcohol **4d** are well tolerated, affording high yields of the desired arylated products **5c** and **5d**, respectively. Here again, although alkenes[2] and hydroxyl[4] groups are known to react with benzyne, no reaction with these functionalities was observed. Of particular interest are the cyclic β-enamino ketones **4g**−**j** which can be arylated

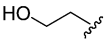
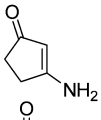
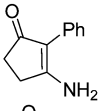
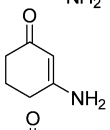
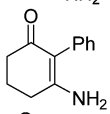
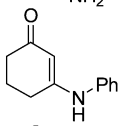
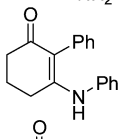
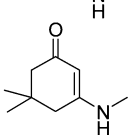
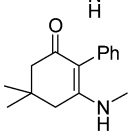
(9) (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918−9919. (b) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309−1319.

(10) (a) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215−218. (b) Majumdar, K. C.; Sarkar, S. *Synth. Commun.* **2004**, *34*, 2873−2883. (c) Tseng, C.-M.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2004**, *60*, 12249−12260.

(11) Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Synthesis* **2002**, 1454−1458.

Table 3. C-Arylation of β-Enamino Ketones with Benzyne[a]



Entry	β-Enamino Ketone		Product		Yield (%)[b]
1	R = Ph	**4a**	**5a**		82
2	R = 	**4b**	**5b**		87
3	R = 	**4c**	**5c**		88
4	R = 	**4d**	**5d**		90
5	R^2 = Me	**4e**	**5e**		92[c]
6	R^2 = Ph	**4f**	**5f**		93[c]
7		**4g**		**5g**	86
8		**4h**		**5h**	87
9		**4i**		**5i**	77
10		**4j**		**5j**	58

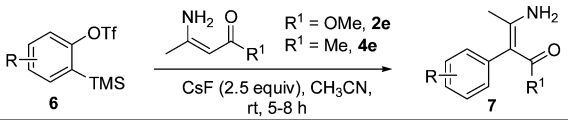
[a] Reaction conditions: 1.25 equiv of *ortho*-silyl aryltriflate **1**, 1 equiv (0.4 mmol) of the β-enamino ketone **4**, 2.5 equiv of CsF, 0.2 M CH_3CN in a sealed vial at room temperature. [b] Isolated yield. [c] Configuration of the double bond was determined by NOE.

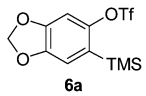
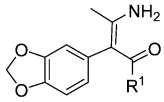
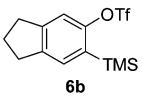
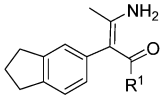
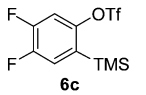
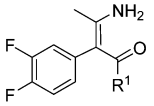
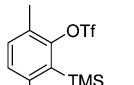
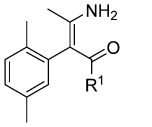
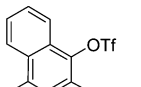
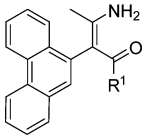
in a similar manner to generate interesting C-arylated products **5g**−**j** in moderate to high yield.

The C-arylation of the β-enamino esters and ketones could also be extended to substituted arynes. As depicted in Table 4, arynes with electron-donating group **6a**, electron-withdrawing group **6c**, sterically crowded **6d**, and bulky arynes **6e** work efficiently to afford good to excellent yields of the C-arylated products **7a**−**j**.

On the basis of the fact that no insertion of aryne into the α-carbon and carbonyl σ-bond of the enamines was observed, we hypothesize that the anion of the initially formed zwitterionic species is rapidly protonated, presumably via an intramolecular proton transfer. To further substantiate this hypothesis, we conducted deuterium labeling experiments. When the reaction of β-enamino ester **2e** and ketone **4e** with *ortho*-silyl aryltriflate **1** (Scheme 1) was quenched with D_2O, no deuterium incorporation was observed on the benzene

Table 4. C-Arylation of β-Enamino Esters and Ketones with Substituted Benzyne[a]

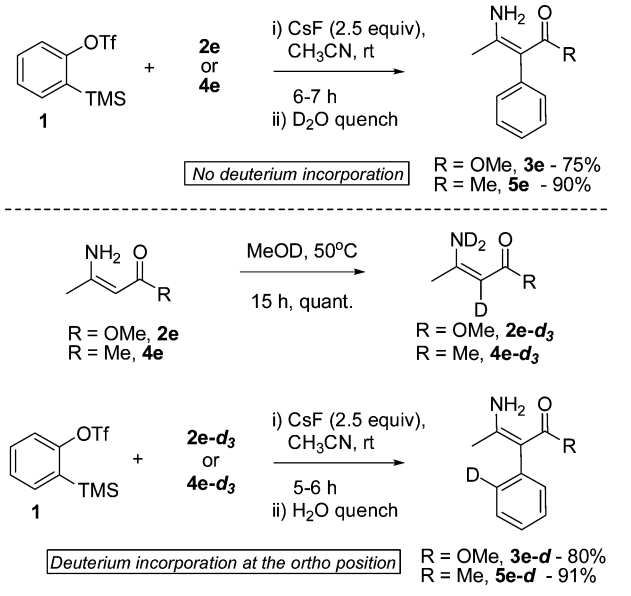


Entry	o-Silyl Aryltrifalte	Product		Yield (%)[b]
1	 **6a**		R^1 = OMe, **7a**	86
			R^1 = Me, **7b**	91
2	 **6b**		R^1 = OMe, **7c**	69
			R^1 = Me, **7d**	80
3	 **6c**		R^1 = OMe, **7e**	77
			R^1 = Me, **7f**	87
4	 **6d**		R^1 = OMe, **7g**	92
			R^1 = Me, **7h**	96
5	 **6e**		R^1 = OMe, **7i**	91[c]
			R^1 = Me, **7j**	91[c]

[a] Reaction conditions: 1.25 equiv of *ortho*-silyl aryltriflate **6**, 1 equiv (0.4 mmol) of the β-enamino ester **2e** or ketone **4e**, 2.5 equiv of CsF, 0.2 M CH_3CN in a sealed vial at room temperature. [b] Isolated yield. [c] Configuration of the double bond was determined by NOE.

ring of **3e** and **5e**, respectively. In a separate experiment, the acidic protons of the β-enamino ester **2a** and ketone **4e** were exchanged for deuterium by stirring in deuterated

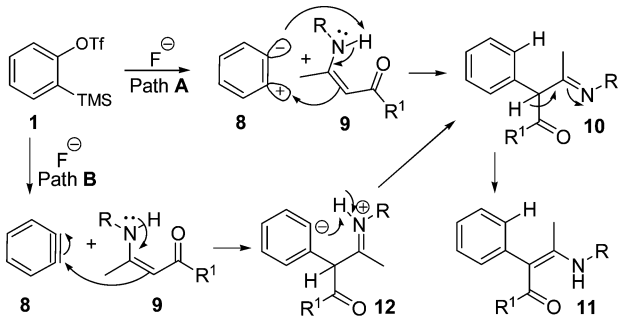
Scheme 1. Deuterium Labeling Experiments



methanol to afford the trideuterated substrates **2e-*d*$_3$** and **4e-*d*$_3$**, respectively (Scheme 1). Upon treatment of substrates **2e-*d*$_3$** and **4e-*d*$_3$** with the benzyne precursor **1**, we were pleased to find that there was quantitative incorporation of deuterium at the *ortho* position of the respective products **3e-*d*** and **4e-*d***. This proves that protonation of the zwitterionic anion is carried out by the β-enamino substrate and not by water during quenching.

On the basis of the deuterium labeling results, we propose two possible mechanistic pathways for the C-arylation of the β-enamino compounds, a concerted (path A) or a stepwise (path B) pathway (Scheme 2). The initial step involves

Scheme 2. Plausible Mechanisms for the C-Arylation of β-Enamino Esters and Ketones with Aryne



generation of the benzyne **8** in the presence of a fluoride anion. In path A, the benzyne **8** can react with the β-enamino carbonyl compound **9** through a concerted aza-ene[12] type reaction to produce the imine intermediate **10** which subsequently tautomerizes to the more stable isomer **11**. On the other hand, in path B, the β-enamino carbonyl **9** can undergo a direct nucleophilic attack on the benzyne **8** to generate the zwitterionic intermediate **12**. The iminium group of **12** is predisposed to transfer its proton to the aryl anion generating the intermediate **10** which after tautomerization would afford the desired product **11**. In addition, because a fluoride anion is a weak base, a pathway involving deprotonation of the N−H proton of **9** to generate the corresponding enamine anion cannot be ruled out.

In summary, we have developed a mild, efficient, and general method for the C-arylation of β-enamino esters and ketones with arynes. The reaction tolerates a variety of substitutions and functionalities and provides arylated products in moderate to excellent yield. Moreover, functionalities that are known to react with arynes such as amino, alcohol, alkene, and furan are well tolerated. This methodology provides a facile and direct access to a variety of substituted aromatic β-enamino esters that could potentially be transformed into chiral β-amino acids.[9] Further studies on the substrate scope with other β-enamino compounds are in progress and will be reported in due course.

Acknowledgment. The authors gratefully acknowledge Chun Sing Li, Cameron Black, and Nicolas Lachance for their technical support and helpful discussions. We also thank Dan Sorensen and Laird Trimble (Merck Frosst) for NMR experiments.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL063057K

(12) (a) Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347−360. (b) Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. *Tetrahedron Lett.* **1998**, *39*, 9237−9240. (c) For ene reaction of arynes with alkynes, see: Jayanth, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 2232−2233.