Lewis Acid Catalyzed Reaction of Aromatic Vinyl Halides with Aromatic Aldehydes: A Novel Aldol-type Condensation Mimic

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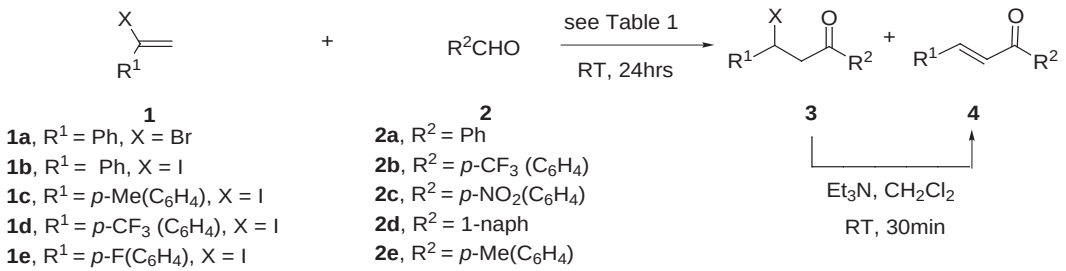
Abstract: In the presence of catalytic amounts of Lewis acid, aromatic α-vinyl halides readily undergo reaction with aromatic aldehydes at ambient temperatures to give a variety of substituted *trans*-chalcones in moderate to excellent yields. These compounds are potentially useful synthetic intermediates for organic synthesis as well as compounds of significance in terms of their ability to exhibit a wide spectrum of biological activity. This is the first reported example in which haloalkenyl derivatives other than metallooxyalkenes can participate in the Mukaiyama-aldol type carbon-carbon formation reaction.

Key words: Lewis acid, catalysis, α-halostyrenes, aromatic aldehydes, substituted *trans*-chalcones

The emergence of the Mukaiyama-aldol protocol over the latter part of the 20th century has established the aldol reaction as one of the most powerful tools in organic synthesis.[1] Relying on the use of Lewis acid catalyzed metal generated enol ether nucleophiles, the ability to furnish important synthetic intermediates and target compounds in an expedient and stereoselective manner has played a significant role in its rise to prominence. To date, much attention within this field has primarily focused upon the development of this particular aspect of the reaction with the view of optimizing yields and stereoselectivity. In studies directed towards exploring the possibility of related reactions, we report herein a novel aldol-type condensation mimic. This involved a variety of aromatic vinyl halides and aldehydes to readily undergo reaction when subjected to catalytic amounts of Lewis acid at ambient temperatures to give the corresponding diaryl propenones in moderate to excellent yields.[2] This new one step carbon-carbon bond formation procedure not only delivers potentially useful synthetic intermediates for organic synthesis but also provides ease of access to a class of compounds known to exhibit antibacterial, antiviral, gastric protectant, antimutagenic, retinoid, antimitotic and antiinflammatory activities in their own right.[3]

The reaction between α-bromostyrene **1a** and benzaldehyde **2a** was initially chosen to establish the optimum temperature, solvent and catalyst conditions (Scheme 1 and Table 1). Thus, whilst pleased that the reaction proceeded smoothly at high temperature in the absence of both a catalyst and solvent to give *trans*-chalcone **4a**[4] in good yield (entry 1), it gave us greater satisfaction to achieve similar results at room temperature in a few cases with the introduction of a variety of stiochiometric amounts of Lewis acid catalysts in CH_2Cl_2 (entries 2-10). Under these applied conditions optimum yields were obtained when the reaction was carried out with $BF_3{\cdot}Et_2O$ (entry 4).

With the catalyst of choice established, a variety of solvents were surveyed to establish the influence of the reaction medium on yield. In comparing the yield obtained for the model study carried out in CH_2Cl_2 (entry 4), the use of relatively less polar solvents furnished **4a** in moderately lower yields (entries 11, 12). As for solvents of relatively higher polarity, with the exception of MeCN (entry 13), either trace product formation was observed or no reaction was detected (entries 14, 15). In contrast, optimum yields were obtained when the reaction was carried out in the absence of solvent with the reaction requiring only a catalytic amount of $BF_3{\cdot}Et_2O$ (20mol%). Under these conditions, a mixture of the β-halo ketone intermediate **3a**[5] and **4a** in 19% and 66% yield respectively was obtained with the former readily converting to **4a** upon purification (entry 16).[6]



Scheme 1

Table 1 The Reaction of α-Bromostyrene **1a** with Benzaldehyde **2a** under Various Conditions

Entry	Solvent (1M)	Lewis Acid	Yield/%[a] **4a**
1	-[b]	-	70[c]
2	CH_2Cl_2	$ZnCl_2$[d]	66
3	CH_2Cl_2	$HfCl_4$[d]	72
4	CH_2Cl_2	$BF_3{\cdot}Et_2O$[d]	73(72)[e]
5	CH_2Cl_2	$InCl_3$[d]	trace
6	CH_2Cl_2	$SnCl_4$[d]	decomposition
7	CH_2Cl_2	$AlCl_3$[d]	decomposition
8	CH_2Cl_2	$ZrCl_4$[d]	decomposition
9	CH_2Cl_2	$TiCl_4$[d]	decomposition
10	CH_2Cl_2	$NiCl_2$[d]	no reaction
11	toluene	$BF_3{\cdot}Et_2O$[d]	50
12	hexane	$BF_3{\cdot}Et_2O$[d]	53
13	MeCN	$BF_3{\cdot}Et_2O$[d]	40
14	EtOH	$BF_3{\cdot}Et_2O$[d]	trace
15	DMF	$BF_3{\cdot}Et_2O$[d]	no reaction
16	-	$BF_3{\cdot}Et_2O$[e]	66[f]

[a]GC yields.
[b]Carried out at 120 °C for 24 h.
[c]Isolated yield.
[d]1 molar equivalent.
[e]0.2 molar equivalent.
[f]**3a** was also obtained in 19% yield.

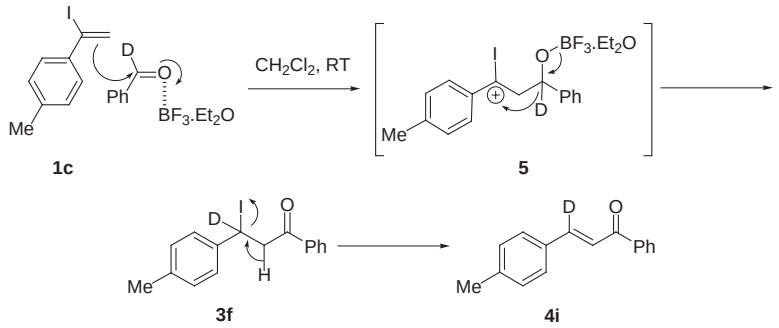
The generality of the present novel reaction was next investigated. In employing either CH_2Cl_2 or solvent-free conditions in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ (20mol%), a variety of other aromatic vinyl halides **1** and aldehydes **2** proceeded in a similar manner to give the corresponding product(s) **3** and **4** in moderate to excellent yields (Table 2). Reaction of α-iodostyrene **1b**[7] with benzaldehyde **2a**, for example, afforded *trans*-chalcone **4a** exclusively as the sole product in 84% yield (entry 1). Similarly, the reaction of **1a** with aromatic aldehydes bearing electron withdrawing groups (EWG) afforded mixtures of the corresponding products **3b** and **4b**, and **3c** and **4c** in excellent overall yields (entries 2-3). In both cases, the conversion of the former to the latter was readily achieved in quantative yields on addition of Et_3N. In comparison, the reaction of **1a** with aromatic aldehydes bearing electron donating groups (EDG) proceeded to give the corresponding adducts **4d** and **4e** in only moderate to good yields (entries 4-5). Conversely, the opposite was observed for reactions of a variety of aromatic vinyl halides bearing either EDG or EWG with benzaldehyde **2a**. Thus, in the case of reaction of **1c** bearing a methyl EDG with **2a**, the corresponding adduct **4f** was furnished in 61% yield despite its relative instability under acidic conditions (entry 6). In contrast, the analogous reaction of **2a** with **1e** bearing an F EWG gave **4h** in only 44% yield whilst reaction of **2a** with **1d** bearing an even stronger EWG in the form of CF_3 gave no reaction (entries 7, 8).

In an attempt to understand the mechanism of our novel vinyl halide-aldehyde protocol, the reaction of **1c** with benzaldehyde-*d*[8] was undertaken to give the deuterated product **4i** in 21% yield (Scheme 2). ^{1}H NMR spectroscopic analysis of **4i** enabled its *d*-content to be determined to be nearly 100%. This was achieved by observing

Table 2 The Reaction of a Variety of Substituted Aromatic Vinyl Halides **1** and Aldehydes **2**

Entry	Vinyl halide **1**	Aldehyde **2**	Product(s) **3**:**4**	Yield **3**:**4**%
1	**1b**	**2a**	**4a**	84
2	**1a**	**2b**	**3b** *p*-$F_3C(C_6H_5)$ Ph; **4b** *p*-$F_3C(C_6H_5)$ Ph	22:72
3	**1b**	**2c**[a]	**3c** *p*-$O_2N(C_6H_5)$ Ph; **4c** *p*-$O_2N(C_6H_5)$ Ph	20:57
4	**1b**	**2d**[a]	**4d**	58
5	**1b**	**2e**[a]	*p*-$Me(C_6H_5)$ Ph **4e**	34
6	**1c**[7]	**2a**[b]	Ph (C_6H_5)*p*-Me **4f**	61
7	**1d**[7]	**2a**	Ph (C_6H_5)*p*-CF_3 **4g**	nr[c]
8	**1e**[7]	**2a**[a]	Ph (C_6H_5)*p*-F **4h**	44

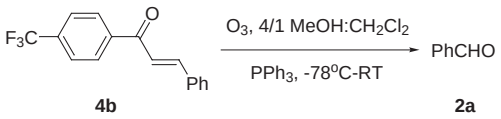
[a]Used as a 1M solution in CH_2Cl_2.
[b]Used as a 2M solution in CH_2Cl_2.
[c]No reaction under a variety of conditions.



Scheme 2

the complete absence of the AB system in **4i**, as seen to be present in its non-deuterated analogous adduct **4f**,[9] along with the replacement of this splitting pattern with a singlet signal at δ7.52. More significantly, this analysis also strongly implied the most probable involvement of an exclusively intramolecular hydrogen transfer step at some point in the reaction mechanism.[10] Consequently, on the basis of this data, we reasoned that the mechanism of our present reaction proceeded via the cationic intermediate **5** generated from the initial 1,2-addition of the vinyl halide **1** to the aldehyde **2**. Preferential intramolecular rearrangement of this reactive intermediate in the form of a 1,3-hydride shift then furnished the more stable β-halo ketone **3**. The isolation of **3** (Table 1, entry 16 and Table 2, entries 2-3) in a few cases, in turn, augmented the credibility of our proposed mechanism. The α, β-unsaturated carbonyl product **4** is then finally afforded upon subsequent hydrogen halide elimination, the rate of which is further enhanced when exposed to basic conditions (Scheme 2).

In order to determine the structure of the product unambiguously, the ozonolysis of **4b** was carried out under standard conditions (Scheme 3). As anticipated, in obtaining benzaldehye **2a** as the sole product, this result also confirmed the structure of the aldol-type product.



Scheme 3

In conclusion, we have demonstrated a novel aldol-type condensation mimic that allows access to a variety of substituted diaryl α-halopropanones **3** and biologically active *trans*-chalcones **4** based on the facile Lewis acid mediated reaction of aromatic vinyl halides with aldehydes at ambient temperatures. We have also provided strong experimental evidence to propose a plausible reaction mechanism for this new transformation. Although the scope of the present novel reaction is limited to aromatic derivatives at the present stage, this is the first reported example in which alkenyl derivatives other than metallooxyalkenes can participate in the Mukaiyama-aldol type carbon-carbon formation reaction.

Acknowledgement

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(5) For a comparison of spectroscopic data, refer to: Le Roux, C.; Gaspard-Iloughmane, H.; Dubac, J. *J. Org. Chem.* **1994**, *59*, 2238-2240.

(6) *Typical procedure*: To an argon flushed solution of α-bromostyrene **1a** (0.5mmol) and benzaldehyde **2a** (0.5mmol) was added $BF_3{\cdot}Et_2O$ (0.1mmol) at r.t. and allowed to stir at this temperature for 24 h. The reaction mixture was then quenched with water, extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$ and

filtered. Concentration and purification by recrystallization (CH_2Cl_2/n-hexanes) gave the bromide intermediate **3a**, followed by silica gel chromatography and recycle preparatory HPLC for analytical purposes, to furnish *trans*-chalcone **4a**. **3a**: ^{1}H NMR (300 MHz, [$CDCl_3$], 25 °C, TMS) 7.94 (m, 2H, ArCH), 7.25-7.61 (m, 8H, ArCH), 5.67 (dd, ^3J(H,H) 7.9 & 6.0Hz, 1H, PhC(I)H), 4.11 (dd, ^3J(H,H) 17.5 & 8.1Hz, 1H, C(I)CH), 3.80 (dd, ^3J(H,H) 17.5 & 6.0Hz, 1H, C(I)CH); MS (70V): m/z (%): 290 (3) [M+H], 105 (100) [C_7H_6O-H]; HRMS: Calcd. for $C_{15}H_{13}BrO$: 288.0150. Found: 288.0155; **4a**: ^{1}H NMR (300MHz, [$CDCl_3$], 25°C, TMS) 7.94-8.20 (m, 1H, ArCH), 7.65-7.79 (m, 1H, ArCH), 7.56-7.65 (m, 1H, ArCH), 7.31-7.42 (m, 9H, ArCH & CH = CH); MS (70V): m/z (%): 208 (100) [M·]; HRMS: Calcd. for $C_{15}H_{12}O$: 208.0888. Found: 208.0890

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(9) **4f**: ^{1}H NMR (300 MHz, [$CDCl_3$], 25 °C, TMS) 7.87 (d, ^3J(H,H) 8.3Hz, 2H, ArCH), 7.74 (d, ^3J(H,H) 15.7Hz, 1H, C = CH), 7.57 (dd, ^3J(H,H) 6.0 & 4.0Hz, 2H, ArCH), 7.47 (d, ^3J(H,H) 15.7Hz, 1H, CH = C), 7.33 (dd, ^3J(H,H) 5.6 & 2.4Hz, 3H, ArCH), 7.23 (d, ^3J(H,H) 8.1Hz, 2H, ArCH), 2.36 (s, 1H, CH_3); **4i**: ^{1}H NMR (300MHz, [$CDCl_3$], 25°C, TMS) 7.92 (d, ^3J(H,H) 8.1Hz, 2H, ArCH), 7.61-7.65 (m, 2H, ArCH), 7.52 (s, 1H, CH = C), 7.38-7.41 (m, 3H, ArCH), 7.23-7.30 (m, 2H, ArCH), 2.42 (s, 1H, CH_3).

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