



A highly stereoselective, novel coupling reaction between alkynes and aldehydes

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Abstract—In the presence of indium triflate or gallium chloride, a novel coupling between internal alkynes and aldehydes occurred to give unsaturated ketones and [4+1] annulation products. © 2002 Elsevier Science Ltd. All rights reserved.

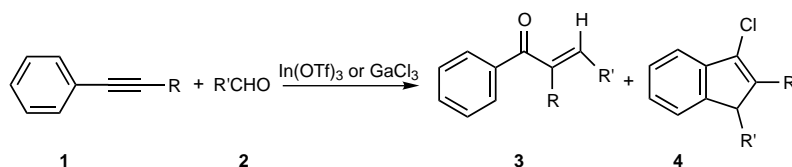
Recently, there has been a considerable interest in indium¹ and gallium² mediated reactions. Coupling reactions of alkynes (and alkynylmetallic reagents) and aldehydes are important transformations in organic synthesis as they generate new carbon–carbon bonds. Recently, progress has been made on addition of terminal acetylenes to aldehydes or ketones and the products are often the propargyl alcohols.³ Herein, we report a hitherto unknown coupling reaction of phenyl alkynes (internal alkyne) **1** with variety of aldehydes **2** resulting in α,β -unsaturated ketones **3** and [4+1] annulation products **4** (Eq. (1)). The major product turns out to be a convenient alternative to Wittig reaction⁴ and aldol reaction.⁵ The traditional Wittig reaction involves the use of reactive phosphorus ylides and aldol condensation often requires an enolate precursor to achieve the desired regioselectivity.

Initially, as an addition to our ongoing efforts to carry out organic reactions in water,⁶ we explored the possibility of coupling aldehydes with phenyl acetylenes to generate propargyl alcohols. Out of several Lewis acids and transition metal catalysts being screened, a completely unexpected condensation product **3** was obtained with indium triflate as a catalyst.⁷ Subsequently, efforts were made to increase the yield of this novel condensation product by using valeraldehyde as a

standard. In water alone aldehydes underwent trimerization so fast that very little coupling product was observed. The use of basic media could not prevent the trimerization. Although a 50:50 mixture of H₂O:TFA gave us the desired product, the yields were poor due to competing reactions such as homo-aldol-condensation of aldehydes and hydrolysis of phenyl acetylene (resulting in acetophenone). The results of these attempts are shown in Table 1. The reaction yields could not be improved when carried out in organic solvents.

It is at this stage when we tried gallium trichloride as a mediator. Although, gallium trichloride has been used in organic synthesis for several decades, there has been no report to our knowledge about its catalytic power to trigger carbon–carbon bond formation between simple alkynes and aldehydes. However, recent reports elucidating its reactivity towards triple bonds⁸ triggered our interest to explore the possibility of using gallium trichloride to promote C–C bond formation.

We were pleased to observe that it was indeed a powerful catalyst to enable C–C bond formation in organic solvents. When a catalytic amount of gallium trichloride (<5%) was added to a methylene chloride solution of 1-phenylpropyne and aldehydes, the reaction gave the α,β -unsaturated ketones **3** and the corresponding



(1)

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Table 1. Indium salt-catalyzed coupling of 1-phenylpropyne with aldehyde

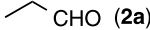
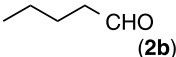
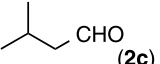
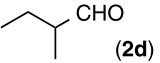
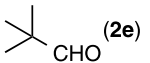
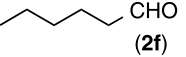
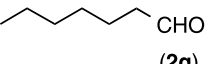
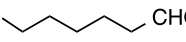
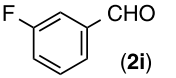
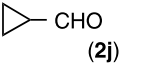
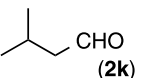
Entry	Aldehyde	Solvent	Catalyst (mol%)	3 yield (%) ^a
1	Valeraldehyde	H ₂ O	In(OTf) ₃ (10)	<10 ^b
2	Valeraldehyde	H ₂ O	In(OTf) ₃ (143)	22
3	Valeraldehyde	H ₂ O	InCl ₃ (5)	0
4	Valeraldehyde	TFA:H ₂ O (1:1)	In(OTf) ₃ (2)	30
5	Trimethylacetaldehyde	TFA:H ₂ O (1:1)	In(OTf) ₃ (70)	40

All reactions were carried out overnight at rt under an air atmosphere.

^a Isolated yields were reported.

^b Estimated by ¹H NMR measurement of the crude reaction mixture.

Table 2. GaCl₃-mediated coupling of phenyl alkynes with aldehydes

entry	phenyl alkyne (1)	RCHO (2)	yield (%)		total yield (%) ^a
			3	4	
1	Ph—C≡C—Me	 CHO (2a)	60(3a)	<5(4a)	65
2	Ph—C≡C—Me	 CHO (2b)	53(3b)	19(4b)	72
3	Ph—C≡C—Me	 CHO (2c)	65(3c)	13(4c)	78
4	Ph—C≡C—Me	 CHO (2d)	55(3d)	12(4d)	67
5	Ph—C≡C—Me	 CHO (2e)	47(3e) ^b	7(4e)	54
6	Ph—C≡C—Me	 CHO (2f)	46(3f)	24(4f)	70
7	Ph—C≡C—Me	 CHO (2g)	35(3g)	22(4g)	57
8	Ph—C≡C—Me	Br—  CHO (2h)	25(3h)	10(4h)	35
9	Ph—C≡C—Me	 CHO (2i)	18(3i)	6(4i)	24
10	Ph—C≡C—Pr	 CHO (2j)	40(3j)	- ^c	40
11	Ph—C≡C—Pr	 CHO (2k)	64(3k)	<4(4k)	68

All reactions were carried out at r.t. in CH₂Cl₂; a. Isolated yields were reported; b. *E:Z* = 15:1, and in all the other cases, *E:Z* > 15:1; c. no significant product could be isolated; entry 7 was carried out at -78°C and warmed to room temperature.

chlorine containing cyclized product **4**; however, the conversion was poor. When the amount of gallium trichloride was increased to ca. 80 mol%, the reaction proceeded smoothly and almost went to completion in 1 h. Subsequently a variety of aldehydes and alkynes were examined for this novel coupling. In each case, phenylalkyne **1** reacted with aldehyde **2** to give primarily the aldol-condensation type product **3**. Except for valeraldehyde and hexanal that were subjected to only 4 h of stirring, all other aldehydes in Table 2 were allowed to react overnight to ensure completion of the reaction.⁹ Aliphatic alkynes gave complicated mixtures. The *trans*:*cis* (or *E*:*Z*) ratios¹⁰ for all substrates were >15:1 (except for entry 5, *E*:*Z*=15:1) based upon both GC/MS and ¹H NMR measurements of the crude reaction mixture.

In summary, a novel coupling of alkynes with aldehydes mediated by indium triflate and gallium trichloride was discovered to generate aldol-condensation products with excellent stereo control and [4+1] annulation products. Currently, efforts are being undertaken to refine the conditions for exclusive formation of either product. The scope and mechanism of this novel coupling is currently under investigation.

Acknowledgements

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- Typical experimental procedure*: 1-Phenylpropyne (38.2 mg, 0.32 mmol) and isovaleraldehyde **2c** (47.7 mg, 0.55 mmol) were dissolved in 2.7 ml of methylene chloride. To this solution GaCl₃ (0.05 g, 0.28 mmol) (as the salt is very moisture sensitive, the weight may not be accurate) was added. The solution turned reddish black instantaneously. The reaction vessel was capped with a septum and sealed with parafilm. After 10 h of stirring, the reaction mixture was concentrated in vacuo. The crude materials were purified by column chromatography on silica gel (with varying amounts of hexane:ethyl acetate as eluent) to give the α,β -unsaturated ketone **3c** (43 mg, yield 65%) and the cyclized product **4c** (10 mg, yield 13%).
- The structures of the products were determined by IR, GC/MS, ¹H and ¹³CNMR. The stereochemistry of **3** was determined by comparing the ¹H NMR data for the known (and the unknown) olefins with those found in the literature. For the disubstituted olefins -CH=CH-: typically, *E*: 6.88 (dt, *J*=15.4, 1.5 Hz, 1H), 7.07 (dt, *J*=15.4, 6.9 Hz, 1H); *Z*: 6.33 (dt, *J*=11.6, 7.4 Hz, 1H), 6.80 (dt, *J*=11.6, 1.8 Hz, 1H). For the trisubstituted olefins -CH=CRCO: typically, *E*: δ 6.3 (tq, *J*=7.4, 1.4 Hz, 1H); *Z*: δ 5.7 (tq, *J*=8.0, 1.6 Hz, 1H). The olefins **3c**, **3d**, **3h**, **3j**, **3k** and the cyclization products **4** are new compounds.