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A Practical Synthesis of Phenylpropargyl Aldehyde from Phenylacetylene and *N*-Formylmorpholine

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Abstract:

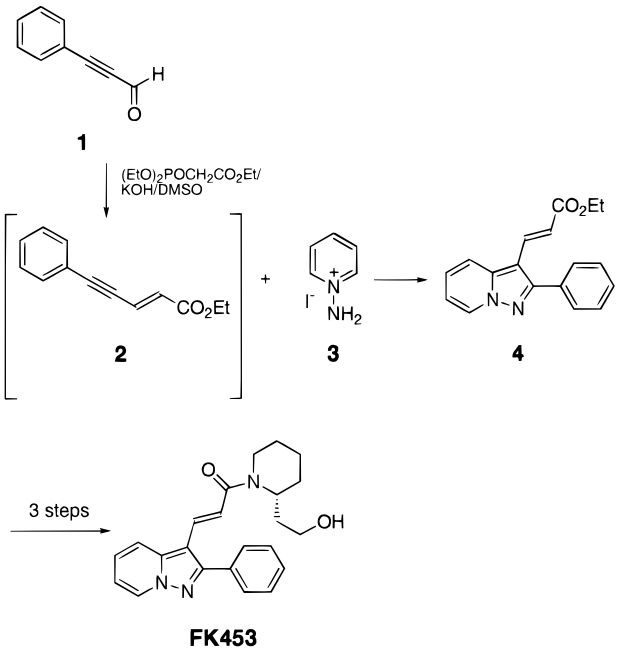
A synthesis of phenylpropargyl aldehyde is described employing formylation of a phenylacetylenic Grignard reagent with *N*-formylmorpholine. This method afforded the product in excellent yield.

Results and Discussion

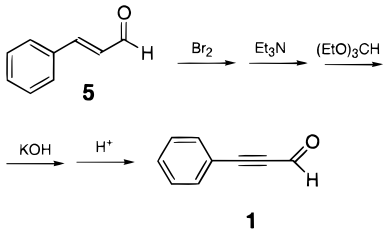
In a previous paper[1] we described a practical synthesis of FK453, a novel nonxanthine adenosine A_1 receptor antagonist *via* (*E*)-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-acryloylate (**4**), the product of a 1,3-dipolar cycloaddition reaction between alkyne (**2**), prepared from phenylpropargyl aldehyde (**1**), and 1-aminopyridinium salt (**3**) (Scheme 1). For the first scale up trial, aldehyde (**1**) was synthesized from *trans*-cinnamaldehyde (**5**) by a slight modification of the reported method[2] (Scheme 2). This process was satisfactorily scaled up; however, several serious drawbacks were noted from the viewpoint of the final production procedure. One problem was that aldehyde (**1**) and the various intermediates are of a highly irritant nature, such that attention must be paid to avoid contact with these agents. A more fundamental problem was that aldehyde (**1**) prepared by this route contained small amounts of impurities, which were suspected to prompt decomposition of **1**. In effect, whilst quantitative purification by distillation on a laboratory scale was possible, about 28% of the aldehyde decomposed and/or polymerized to yield intractable tarry byproducts on a 100 kg scale.[1] A DTA (differential thermodynamic analysis) study indicated that aldehyde (**1**) started to decompose at 96 °C (Figure 1). The stability test under adiabatic conditions also presented the same profile. According to these results, purification by distillation (91−93 °C/6 mmHg)[1] might be dangerous and should be excluded from larger scale synthesis. Thus, this procedure had to be modified to a more safe and efficient process.

As an alternative approach to aldehyde (**1**), formylation of phenylacetylene (**6**) was attractive (Scheme 3). Several methods for coupling Grignard reagents with formamides are known in the literature.[3−7] In 1978, Comins and Meyers reported excellent results converting phenylacetylenic Grignard reagent (**7**) to **1** using 2-(*N*-formyl-*N*-methyl)aminopyridine.[3] The success of their method was ascribed to the ready formation of a six-membered chelate ring, which prevented further reaction with Grignard reagent. Fréchet *et al*. also emphasized the role of chelation in formylation of Grignard reagents with several *N*-formylamines.[4] The improved yield using 2-(*N*-formyl-*N*-methyl)aminopyridine compared with using *N*-formylpiperazine or DMF was attributed to inhibition of secondary alcohol formation resulting from further reaction with Grignard reagent. On the other hand, reports from Olah and Arangashi have appeared in which excellent results were obtained by using DMF,[5] *N*-formylpiperazine,[6] and *N*-formylmorpholine.[7] Quite

Scheme 1. **Route to FK453 from phenylpropargyl aldehyde (1)**



Scheme 2. **Route to phenylpropargyl aldehyde (1) from *trans*-cinnamaldehyde (5)**



(1) Zanka, A.; Uematsu, R.; Morinaga, Y.; Yasuda, H.; Yamazaki, H. *Org. Process Res. Dev.* **1999**, *3*, 389.
(2) Allen, C. F. H.; Edens, C. O., Jr. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 731.
(3) Comins, D.; Meyers, A. I. *Synthesis* **1978**, 403.
(4) Amaratunga, W.; Fréchet, J. M. J. *Tetrahedron Lett*. **1983**, *24*, 1143.
(5) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *Synthesis* **1984**, 228.
(6) Olah, G. A.; Arvanaghi, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 878.
(7) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *J. Org. Chem*. **1984**, *49*, 3856.

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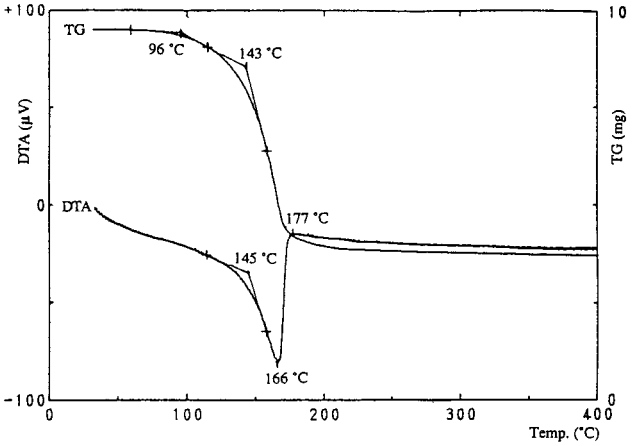
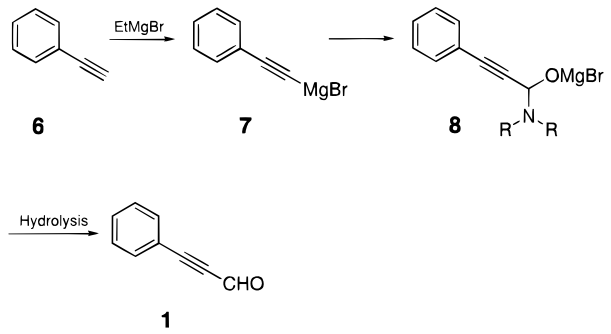


Figure 1. **DTA study of aldehyde (1).**

Scheme 3. **Route to phenylpropargyl aldehyde (1) from phenylacetylene (6)**



recently, an efficient synthesis of **1** was described by Journet *et al*.[8] The mild conditions for hydrolysis of the incipient intermediate (**8**) were considered essential to prevent further reaction of the acetylenic aldehyde with dimethylamine. However, despite these excellent results, the requirement for a large amount of phosphate solution and MTBE for back extraction are problematic from the viewpoint of high throughput, which is one of the main issues for a cost-effective synthesis.

Herein, I wish to report the results of endeavours aimed at efficient formylation of phenylacetylenic Grignard reagent (**7**), without side-reactions. Whilst 2-(*N*-formyl-*N*-methyl)-aminopyridine was not commercially available and required several steps for preparation, DMF is inexpensive and readily available in large quantities. Thus, our process research was initiated by coupling Grignard reagent (**7**) with DMF, focusing on optimizing the hydrolysis conditions. As pointed out by Olah and Arvanaghi, no further reaction was involved, and secondary alcohol was not detected when the reaction was carried out with avoidance of an excess of Grignard reagent. However, in our early studies, the yield was low when only a slight excess hydrochloric acid was used in the hydrolysis at 0−5 °C, aimed at avoiding excess use of reagent and further reactions of **1** with dimethylamine. (Table 1, entry 1). As pointed out by previous authors[8] the yield of **1** was greatly affected by the hydrolysis step. Examination of the optimum conditions in the work-up afforded the following results. A higher concentration of hydrochloric acid afforded smooth hydrolysis (entry 2). However, under these conditions, further reaction of the aldehyde (**1**) with hydrogen chloride and/or dimethylamine occurs; thus, the extraction must be conducted quickly after the completion of the reaction (entry 2, 3). Since this could not be done effectively on a large scale, this method was not developed further. On the other hand, reaction at 20−25 °C gave improvement in the yield (entry 4). Despite these excellent results, the obtained aldehyde (**1**) contained small amounts of unknown byproducts and required further purification by distillation. Envisaging avoidance of further reactions, we examined other formamides derived from weakly basic amines. Amongst several formamides, *N*-formylmorpholine was especially attractive, since this pure grade reagent is readily available in large quantities and is easily prepared and inexpensive ($6/kg, in bulk quantities) from BASF Co. The coupling of the Grignard reagent (**7**) with *N*-formylmorpholine proceeded smoothly, and the further reactions in question did not occur at all, regardless of the amount of hydrogen chloride. These excellent results were presumably attributed to the weak basicity of morpholine ($pK_a = 8.3$) compared with that of dimethylamine ($pK_a = 10.7$). Interestingly, the hydrolysis step was complete in only 30 min, whilst 7 h was required in the case of DMF (entry 3, 4, 7, 8). The explanation for this unexpected difference in hydrolysis is not clear at this point, but our best speculation is that morpholine as a weak base enhances smooth hydrolysis under mild conditions, preventing further reactions of **1**. As a result of these findings, the aldehyde (**1**) was synthesized in higher yield (96%, quantitative HPLC) and better quality (98% HPLC area, phenylacetylene: 2% HPLC area) than the product from route A (95% HPLC area, after distillation) and thus could be immediately used in the following step after exchange of solvents.

The ester (**4**) was synthesized in excellent quality (99.8% chemical purity) and good yield (59%) according to the reported method,[1] and no new impurities were identified in the material.

Table 1. **Effect of hydrolysis conditions on the yield after coupling Grignard reagent (7) with *N*-formylamine**

entry	*N*-formylamine	% of HCl (equiv)	temp(°C)/ time (min)	yield (%)[a]
1	DMF	3(2.0)	0/30	34(40)[b]
2	DMF	6(2.0)	20/30	65
3	DMF	6(2.0)	20/120	59
4	DMF	3(2.0)	20/420	81
5	*N*-formylpiperidine	3(2.0)	0/30	43(31)[b]
6	*N*-formylmorpholine	3(2.0)	0/30	88
7	*N*-formylmorpholine	3(2.0)	20/30	94
8	*N*-formylmorpholine	6(2.0)	20/30	96

[a] Yield was determined by quantitative HPLC. [b] Recovered yield from the separated aqueous layer.

Conclusions

In this paper, a practical and facile synthesis of phenylpropargyl aldehyde is described. The use of inexpensive and readily available *N*-formylmorpholine as the formylation

(8) Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427.

reagent and optimized work up conditions gave a product with superior quality to the material from the first pilot plant scale campaign without a distillation purification process.

Experimental Section

Pure grade *N*-formylmorpholine is available in bulk quantities from BASF Co. Phenylacetylene was obtained from Wychem Co. and was distilled before use to remove a small amount of water. All other chemicals were obtained from the usual commercial suppliers.

Phenylpropargyl Aldehyde (1). Ethylbromide (10.7 g, 97.9 mmol) and a small amount of iodine were added to metallic magnesium (28.4 g, 1.17 mol) in dry THF (1000 mL) and heated to 35 °C. After the mixture stirred for 1 h, ethylbromide (128 g, 1.17 mol) was slowly added at about 35 °C, and the solution was refluxed for a further 1 h. Control of exotherm in the reaction was achieved by controlling the addition speed of ethylbromide. Phenylacetylene (**6**) (100 g, 0.979 mol) was added to the prepared Grignard reagent at about 35 °C, after which the reaction was continued at the same temperature until no more ethane was evolved. To the prepared acetylenic Grignard reagent (**7**), which was kept at 35 °C to avoid precipitation, was slowly added *N*-formylmorpholine (226 g, 1.96 mol) at 35 °C. After the mixture stirred for an additional 30 min, this solution was added to 6% hydrochloric acid in water (1000 mL) at <25 °C. After the mixture stirred for 30 min at 20−25 °C, toluene (1000 mL) was added to this reaction mixture. The layers were separated, and the aqueous layer was re-extracted with toluene (500 mL). The combined organic layer was then washed with 10% brine (1000 mL). The organic layer contained 122 g of phenylpropargylaldehyde (**1**) (96% yield) by quantitative HPLC. Removal of solvents afforded phenylpropargylaldehyde (**1**) as an oil (98% HPLC area), identical with authentic material (^{1}H NMR, HPLC).

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