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Technical Notes

Efficient Large-Scale Synthesis of 4-Phenyl-3-butyn-2-one, a Key Intermediate for a Novel Potent Adenosine Antagonist

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Abstract:

Phenylacetylenic Grignard reagent reacts with acetic anhydride under mild conditions to give 4-phenyl-3-butyn-2-one in high yield. This method was applicable to a large-scale synthesis, and optimized reaction conditions have been investigated.

Results and Discussion

Horiai and co-workers[1] have shown that 6-oxo-3-[2-phenylpyrazolo[1,5-*a*]pyridin-3-yl]-1(6*H*)-pyridazinebutyric acid (FK838), an adenosine A1 receptor antagonist, has potent diuretic and anti-hypertensive effects which are useful for the regulation of renal function. We required a large quantity of FK838 (200 kg) for complete biological evaluation. FK838 is prepared *via* the pyrazolo[1,5-*a*]pyridine **3**, the product of a 1,3-dipolar cycloaddition reaction between ketone **1a** and 1-aminopyridinium salt (**2**, Scheme 1). Whilst 4-phenyl-3-butyn-2-one (**1a**) can be purchased from the Aldrich Chemical Co., the required quantity of **1a** (>100 kg) was so large that we decided to investigate practical and inexpensive methods amenable to a large-scale operation. In this paper we describe a simple, practical, optimized method for the synthesis of **1a** that is readily scaled up to 50−100 kg scale.

The most conceptually simple method for the preparation of **1a** would involve acylation of phenylacetylene; however, despite various known methods based on this disconnection, the literature was not helpful in presenting an efficient procedure. Easily prepared metal acetylides such as Li,[2] Mg,[3,4] and Na[5] suffer from poor yields since the high reactivity of the organometallic reagent leads to some undesired products. Furthermore, using heavy metals such as Cu[6] and Zn[7] affords good results, but these methods required tedious procedures and are not favorable from the environmental point of view. Amongst the known methods, Yamaguchi *et al.*[8] and Brown *et al.*[9] have reported a novel synthesis of acetylenic ketones *via* the reaction of alkynylboron compounds in good yields, but this method requires low-temperature conditions (−78 °C), and this was not acceptable to us for a large-scale synthesis.

In order to develop alternative and improved acylating systems for coupling with alkynylmetal species, we examined readily available starting materials and inexpensive preparative methods. Acetyl chloride, *N*,*N*-dimethylacetamide, methyl acetate, and acetic anhydride are inexpensive and commercially available; thus, we investigated the acylating ability of these agents. Regarding activation methods for

Scheme 1. **Route to FK838 from 4-phenyl-3-butyn-2-one (1a)**

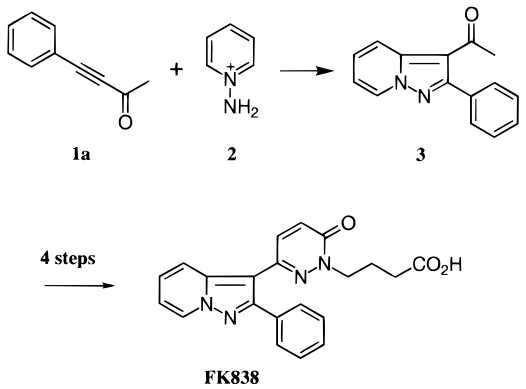

Table 1. **Effect of acylating reagents**

reagent	amount of reagent (equiv)	yield (%)[a]
acetic anhydride	2.5	94[b]
N-acetylmorpholine	2.5	51[b]
DMA	2.5	25[b]
AcOMe	2.5	0
AcCl	1.25	0.4[c]
AcCl	2.50	0.7

[a] Absolute yield was determined by quantitative HPLC. [b] Immediately after the reaction (before addition of MeOH). [c] 40% of carbinol was obtained.

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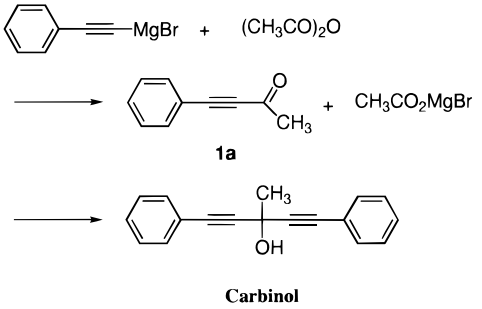
Scheme 2. **Preparation of carbinol**



the phenylacetylene, we selected the sodium acetylide and Grignard reagents, since they are stable and readily prepared on a large scale.

Whilst the reaction of the sodium acetylide with acylating agents suffered from poor yield because of low solubility in THF, the reaction using the phenylacetylenic Grignard reagent revealed several characteristic features of this system (Table 1). Reaction with acetyl chloride afforded mainly an undesired compound, the carbinol resulting from further reaction of **1a** with the acetylide. Reaction using *N*,*N*-dimethylacetamide required an acidic treatment during workup to remove the -NMe_2 group from the adducts. However, under these conditions, further reaction of **1a** with hydrogen chloride and/or dimethylamine occurs; thus, the pH of the reaction mixture must be adjusted quickly to ~6−7. Since this could not be done effectively on a large scale, this method was not pursued. *N*-Acetylmorpholine gave some improvement, but the yield was still unsatisfactory from the point of inexpensive preparation. When an ester was employed, no product was obtained. As can be seen from Table 1, the best result was obtained with acetic anhydride. In previous reports,[4] the low yields in this system are believed to result from reaction of the initially formed ketone with another equivalent of Grignard reagent to form a carbinol (Scheme 2).

In order to avoid this second reaction, the Grignard reagent should be slowly added to a large excess of acetic anhydride at low temperature. In this way, Kroeger and Nieuwland[4] prepared **1a**, but the isolated yield was only 8.3%. On the other hand, from our results, use of a large excess of acetic anhydride may lead to further reaction of the product. Indeed, in the case with 10.5 equiv of acetic anhydride, we did not isolate **1a** at all but recovered only undesired by-products with a small amount of carbinol after workup of the reaction mixture, in spite of an 83% yield at the end of the reaction. Examination of the optimum molar ratio of acetic anhydride afforded the following results. While use of 2.5 equiv of acetic anhydride afforded undesired products, 2.0 equiv of of acetic anhydride provided **1a** selectively in 93% yield (88% in the organic layer and 5% in the aqueous layer). This unexpected difference was due to the reaction of **1a** with acetic acid in the former case. Therefore, these successful results are attributable to decomposition of excess acetic anhydride to acetic acid and methyl acetate by methanol under mild conditions and complete removal of acetic acid in the form of $Mg(OAc)_2$, followed by washing with sodium hydroxide solution in water. Thus,

Table 2. **Effect of Ac_2O amount[a]**

amount of Ac_2O (equiv)	yield (%)[b]	yield (%)[c]	carbinol yield (%)
10.5	83	complex mixture	1.4
5.0	80		2.2
2.5	94	76	2.3
2.0	94	94	2.4
1.25	91		4.3

[a] All reactions were performed on a 50 g (0.49 mol) scale. [b] Absolute yield was determined by quantitative HPLC immediately after the reaction (before addition of MeOH). [c] Absolute yield was determined by quantitative HPLC after workup (after removal of $Mg(OAc)_2$).

Table 3. **Effect of temperature**

temp (°C)	yield (%)[a]	amount of Ac_2O (equiv)	carbinol yield (%)
−5 to +2	94	2.5	3.9
−5 to +2	94	2.0	2.4
−2 to +4	92	2.5	2.4
+3 to +8	88	2.5	5.8

[a] Absolute yield was determined by quantitative HPLC immediately after the reaction (before addition of MeOH).

the optimum molar ratio of acetic anhydride proved to be 2.0 equiv (Table 2).

The reaction temperature is also important. According to the literature,[4] very low temperature conditions such as −25 °C were required in order to avoid the formation of carbinol. However, our results indicate that this reaction goes well even at −5 to +2 °C (Table 3); thus, we need no special equipment for the industrial preparation of **1a**.

We have extended this method for the acylation of several alkynyl derivatives. Based on this optimized method, we were able to prepare silyl alkynyl ketones as well as alkynyl ketones. However, the yields for silyl alkynyl ketones were low. The reasons are not clear, but treatment with water might decompose the product. The results and isolated yields of these ketones are presented in Table 4. ^{1}H NMR spectra of these ketones were in accordance with the assigned structure and literature data.

Conclusion

In conclusion, we have established a practical and facile synthesis of 4-phenyl-3-butyn-2-one (**1a**). The use of an optimum amount of acetic anhydride as the acyl source is a significant improvement over the published procedures and is critical to success. In addition, unlike the conventional methods, the current procedure offers comparatively mild reaction conditions and is suitable for large-scale applications. We have prepared >100 kg of **1a** and, hence, >200 kg of the adenosine A1 receptor antagonist FK838.

Experimental Section

Phenylacetylene is commercially available from the Wychem Co., was of pure grade, and was distilled before use to remove a small amount of water.

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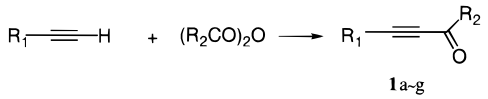
Table 4. **Alkynyl and silyl alkynyl ketones 1a−g prepared**



1a-g

1	R_1	R_2	yield (%)	bp (°C)/ mmHg	lit. bp (°C)/ mmHg	IR (NaCl) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ (ppm)
a	C_6H_5	CH_3	83	80/3.5	76−77/0.9[9]	2200, 1670	2.44 (s, 3H), 7.32−7.57 (m, 5H)
b	C_6H_5	C_2H_5	70	80/0.5	107/0.6[8]	2200, 1670	1.22 (t, 3H, J = 7.34 Hz), 2.70 (q, 2H, J = 7.40 Hz) 7.36−7.60 (m, 5H)
c	C_6H_5	CF_3	49	55/1.0	86−88/16[10]	2200, 1704	7.37−7.71 (m, 5H)
d	^{t}Bu	CH_3	61	60/14	56/15[9]	2222, 1680	1.28 (s, 9H), 2.32 (s, 3H)
e	^{n}Bu	CH_3	80	70/14	68/12[7]	2212, 1676	1.38−1.64 (m, 4H), 2.30 (s, 3H), 2.37 (t, 3H, J = 6.91 Hz)
f	$(CH_3)_3Si$	CH_3	18	54/14	50/15[7]	2152, 1680, 1254	0.23 (s, 9H), 2.34 (s, 3H)
g	$(CH_3)_3Si$	C_2H_5	26	70/32		2150, 1684, 1254	1.11 (t, 3H, J = 7.34 Hz), 2.59 (q, 2H, J = 7.35 Hz)

Preparation of 4-Phenyl-3-butyn-2-one (1a). Ethyl bromide (2.0 kg, 18.3 mol) and a small amount of iodine were added to metallic magnesium (11.3 kg, 465 mol) in dry THF (397 L) and heated to 35 °C. After the mixture was stirred for 1 h, ethyl bromide (53 kg, 486 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 ethyl bromide (3 h was required on this scale). Phenylacetylene (39.7 kg, 389 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. The prepared acetylenic Grignard reagent, which was kept at 35 °C to avoid precipitation, was slowly added to acetic anhydride (79.3 kg, 777 mol) in THF (198 L) at <4 °C over 1 h. After additional stirring for 1 h, to this solution was added MeOH (198 L, 4890 mol). Stirring was continued overnight, and the precipitate was filtered off and washed with THF (198 L). The filtrate was washed with 1 N NaOH (385 L × 1) and brine (300 L × 2). The combined aqueous layers contained 3.0 kg (21 mol) of **1a**, and the organic layer contained 49.6 kg (344 mol) of **1a** (HPLC). The organic layer was evaporated under reduced pressure, to the residue was added CH_2Cl_2 (397 L), and the resulting solution was washed with aqueous $NaHCO_3$ (200 L × 1). This organic layer contained 49.1 kg of 4-phenyl-3-butyn-2-one (**1a**, 87.8% yield), as determined by quantitative HPLC. Removal of solvents afforded **1a** as an oil which was 93% pure by HPLC. An analytical sample was obtained by distillation (78−80 °C/3.5 mmHg; lit.[9] 76−77 °C/0.9 mmHg). Product was identified by comparison with an authentic sample purchased from the Aldrich Chemical Co. by spectroscopic data (NMR, MS): IR (NaCl, ν [cm^{-1}]) 2200, 1670; ^1H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.32−7.57 (m, 5H); MS (EI) m/z 145 $(M + H)^+$.

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