Pergamon

Tetrahedron Letters 41 (2000) 141–144

TETRAHEDRON LETTERS

Thiol addition to aryl propargyl alcohols under mild conditions: an accelerating neighboring group effect

Marjorie See Waters,* Jennifer A. Cowen, J. Christopher McWilliams, Peter E. Maligres and David Askin

Department of Process Research, Merck Research Laboratory, Merck & Co. Inc., PO Box 2000, Rahway, New Jersey 07065, USA

Received 15 October 1999; accepted 28 October 1999

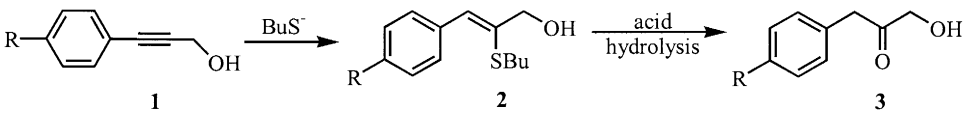
Abstract

Aryl alkynols provide a convenient entry into α-hydroxyketones via thiol addition followed by hydrolysis. Thiols have been added to several non-activated alkynes under mild, basic conditions. A coordinating functional group in close proximity to the triple bond facilitates this reaction.

Keywords: vinyl sulfides; propargylic alcohols; neighboring group effects; hydroxyketones.

α-Hydroxy ketones are versatile intermediates in the synthesis of biologically active compounds, heterocycles, and pharmaceutical products. These compounds have previously been prepared by the selective oxidation of 1,2-diols,[1] often in low yields. Hydroxy ketones have also been prepared from alkenes by treatment with an oxidizing agent and catalytic osmium[2] and with permanganate in acetic acid.[3] In addition, they have been prepared by the rearrangement of α-hydroxy epoxides with palladium.[4] We required hydroxymethyl-α-aryl ketones of the general structure **3** as pharmaceutical intermediates, and sought a method that would not require harsh oxidative conditions. Specifically, we were interested in the 4-cyanobenzyl ketone **3b** (R=CN).

Recently, α-aryl ketones were prepared by the palladium catalyzed arylation of ketones under mild basic conditions; selective reactions were observed with several alkyl and aryl methyl ketones.[5] Unfortunately, we found that α-hydroxy ketones were not good substrates with this method, resulting in no reaction or complex mixtures. Alkynols **1**, already in the required oxidation state, are readily available via Castro–Stephens[6] coupling of the acetylenes with aryl halides; thus the regioselective formal addition of water to **1** would provide the desired hydroxy ketones **3**.



1 **2** **3**

* Corresponding author.

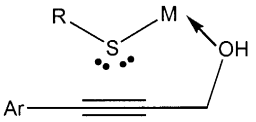
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02040-7

Since addition of water directly to an alkyne typically requires the use of heavy metal catalysts such as mercury or palladium salts,[7] an indirect hydration method was sought. Both alkyl and aryl thiols have been shown to add to alkynes to give vinyl sulfides. With activated alkynes such as α,β-acetylenic esters and ketones, the addition has been performed under basic conditions, using reagents such as KOH[8] and triethylamine.[9] However, for unactivated alkynes, radical initiators,[10] transition metal catalysts[11] and high temperatures[12] have been required. In our work, we have found that under mild, basic conditions thiols add to unactivated aryl alkynols **1**, facilitated by a neighboring group effect.[13] The vinyl sulfides can then be hydrolyzed under a variety of conditions to provide the desired hydroxy-ketone.[14]

We anticipated that the cyanophenyl alkyne **1b** would be sufficiently electron deficient to allow facile nucleophilic addition of a thiol to the alkyne. Reaction of **1b** with *n*-butanethiol and NaOH in acetonitrile at room temperature gave the vinyl sulfide **2b** in 90% yield. Remarkably, reaction of **1a** bearing only a phenyl group without a strongly electron withdrawing functionality with butanethiol and NaOH in acetonitrile at 75°C gave the vinyl sulfide **2a** in 86% yield.[15] As in previous reports, in both cases we saw almost exclusively the *Z* product in the crude ^{1}H NMR (6.8 ppm *Z*, 6.4 ppm *E*). In addition, we saw very high selectivity (100:1) for addition of the thiol β to the phenyl group. The vinyl sulfides **2a** and **2b** were then hydrolyzed using 0.4 M H_2SO_4 in 4:1 ethanol/water at 50°C overnight,[16] giving 1-hydroxy-3-aryl-propan-2-one (**3a** and **3b**) in 83 and 85% yields respectively. The unanticipated ease of thiol addition to **1a** prompted us to study the scope of the reaction with several substituted alkynes.[17] The results are shown in Table 1.

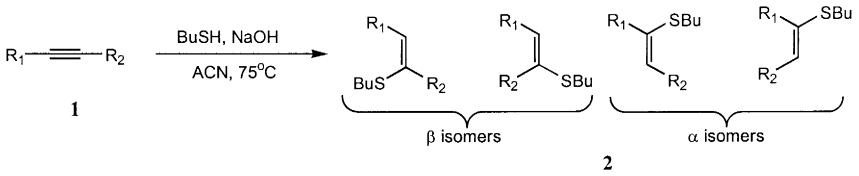
The more electron deficient alkyne (**1c**) reacted with butanethiol exothermically even at room temperature, with the thiol adding exclusively β to the aryl group. However, the less electron deficient alkyne (**1d**) required 5 h at 75°C to react and was slightly less selective in the β/α ratio. Increased branching at the carbon bearing the hydroxyl group (**1e** and **1f**) lead to reduced reactivity. In the tertiary alcohol case, fragmentation to the ketone and acetylide became the major pathway. Surprisingly, even when the moderately electron-withdrawing aryl group was absent, reaction with butanethiol still occurred under the mild, basic conditions. Addition of butanethiol to 2-butyn-1-ol (**1g**) gave 70% conversion after 24 h with only moderate β/α selectivity. With butynediol **1h**, the reaction was complete in only 3 h; in contrast, addition to phenylbutyne **1i** led to only 7% conversion by ^{1}H NMR after 24 h.[13] This profound difference in reactivity shows that the presence of the neighboring alcohol group has a significant effect in the thiolation of alkynes. The data indicates that the neighboring group is relatively weak in directing the regiochemistry, but is clearly accelerating the reaction.

A possible mechanistic explanation for the acceleration in which the alcohol group coordinates with the metal of BuS^-Na^+ is indicated below. Interestingly, when butanethiol was added to **1a** with CsOH or KOH as the base, the reaction was complete in 20 min,[18] NaOH required 90 min, and with LiOH the reaction required over 24 h. The identity of the base had no significant effect on the yield and the *Z/E* and β/α selectivity.



Increasing the distance between the alcohol group and the alkyne through methylene spacers also reduced the reactivity (**1j** and **1k**); nevertheless, both products were isolated after completion in good yields. Phenyl alkynes with other functional groups that can provide coordination to a metal cation showed good reactivity with butanethiol (**1l** and **1m**).[19] In conclusion, aryl alkynols provide a convenient entry into aryl ketones via the vinylic sulfides, avoiding the use of strong oxidizing agents. The base

Table 1
Addition of thiols to alkynes[a]



Entry	Alkyne	R_1	R_2	Time (hrs)	% Yield[b] **2**	*Z*/*E*[c] ratio	β/α[c] ratio
1	**1a**	Ph	CH_2OH	3	86	>100:1	100:1
2	**1b**	4-CN-Ph	CH_2OH	0.25[d]	90	>100:1	>100:1
3	**1c**	3,5-$(CF_3)_2$-Ph	CH_2OH	0.25[d]	98	>100:1	>100:1
4	**1d**	4-MeO-Ph	CH_2OH	5	86	>100:1	38:1
5	**1e**	Ph	$CH(OH)(CH_2)_2CH_3$	10	87	>100:1	100:1
6	**1f**	Ph	$C(OH)(CH_3)CH_2CH_3$	20	27[e]	----	----
7	**1g**	CH_3	CH_2OH	24	42[f]	24:1	1:5
8	**1h**	CH_2OH	CH_2OH	3	51	35:1	----
9	**1i**	Ph	CH_2CH_3	24	7[g]	----	----
10	**1j**	Ph	$(CH_2)_2OH$	17	79	>100:1	75:1
11	**1k**	Ph	$(CH_2)_3OH$	90	67	61:1	100:1
12	**1l**	Ph	CH_2OMe	10	89	32:1	85:1
13	**1m**	Ph	CH_2NH_2	6	57	27:1	>100:1

(a) Reactions were carried out in MeCN (1 mL/mmol) at 75 °C using 1 eq. of NaOH. Reaction progress was monitored by HPLC on a P/E 3 × 3 cartridge column with an 8 minute gradient from 90:10 0.1% H_3PO_4/MeCN to 25:75 at 2 mL/min. The crude reaction was concentrated, diluted with *t*-BuOMe and passed through silica. The filtrates were concentrated to provide the crude product. Other thiols such as PhSH and EtSH were found to similarly add to alkynes **1a** and **1b**. (b) Isolated yield after silica gel chromatography unless otherwise indicated. (c) Ratios determined by ^{1}H NMR (integration of vinylic protons) of the crude materials passed through silica (as solutions in *t*-BuOMe). The vinylic protons had very distinctive shifts, 6.7-6.5 β,*Z*; 6.5-6.3 β,*E*; 6.2-6.0 α,*Z*; 5.8-5.7 α,*E*. (d) This reaction was exothermic and run at 20 °C with slow addition of BuSH. Reaction at 75 °C lead to decomposition. (e) The low yield is due to significant formation of the fragmentation product in 42% isolated yield. (f) The conversion determined by ^{1}H NMR (integration of methyl and hydroxymethylene protons) after 24 hours was 70%. (g) Conversion as determined by ^{1}H NMR (integration of methyl and methylene protons). The vinyl sufide was not isolated.

catalyzed addition of thiols to alkynes takes place under mild conditions due to acceleration by the neighboring hydroxyl group.

Acknowledgements

We wish to thank Peter Dormer for his NMR support.

References

1. Sakata, Y.; Ishii, Y. *J. Org. Chem.* **1991**, *56*, 6233–6235. Navarro, M.; De Giovani, W. F.; Romero, J. R. *Tetrahedron* **1991**, *47*, 851–857. Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169–8178.

2. Murahashi, S. I.; Naota, T.; Hanaoka, H. *Chem. Lett.* **1993**, *10*, 1767–1770. Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, *9*, 1499–1502.
3. Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, 520–521.
4. Vankar, Y. D.; Chaudhuri, N. C.; Singh, S. P. *Synthetic Commun.* **1986**, *16*, 1621–1626. Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1994**, *59*, 7195.
5. Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383.
6. Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163; Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 3313–3315.
7. Hudrlik, P. F.; Hudrlik, A. M. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, Ed.; John Wiley & Sons: 1978; Part 1, Chapter 7. Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127–3130.
8. Wadsworth, D. H.; Detty, M. R. *J. Org. Chem.* **1980**, *45*, 4611–4615. Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1974**, 705–708.
9. Dieter, R. K.; Silks, L. A. III; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679–4692.
10. Galambos, G.; Csokasi, P.; Szantay, C. J.; Czira, G.; Szantay, C. *Heterocycles* **1994**, *38*, 1459–1464. Montevecchi, P. C.; Navacchia, M. L. *Tetrahedron Lett.* **1998**, *39*, 9077–9080.
11. Kuniyasu, H.; Ogawa, A.; Sato, K. I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 5902–5903. Ishino, Y.; Masaoka, T.; Hirashima, T. *Chem. Lett.* **1990**, *7*, 1185–1188. Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108–5114.
12. Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, *9*, 2103–2109.
13. On a similar system, Schroth found that phenylmethanethiol added to 1-(2-thiomethoxy)-phenyl-1-propyn-3-ol using KOH in DMF, while addition of the same thiol to an alkyne in which the alcohol is replaced by a methyl group required heating to reflux with KOH and 18-crown-6 in benzene/water: Schroth, W.; Jordan, H.; Spitzer, R. *Tetrahedron Lett.* **1995**, *36*, 1421–1424.
14. Grobel, B.; Seebach, D. *Synthesis* **1977**, 357–402.
15. Preparation of **2a**: 1-Phenyl-1-propyn-3-ol (0.67 g, 5.0 mmol) and powdered NaOH (0.21 g, 5.2 mmol) were combined in 5 mL of MeCN. Butanethiol (0.70 mL, 6.5 mmol) was added via syringe. The slurry was heated to 75°C for 3 h. The crude reaction was concentrated to a dark orange oil. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes) to provide **2a** as a colorless oil (0.96 g, 86% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.63–7.24 (m, 5H), 6.82 (s, 1H), 4.35 (s, 2H), 2.77 (t, 2H, 7.26 Hz), 2.28 (s, 1H), 1.53 (m, 2H), 1.36 (m, 2H), 0.87 (t, 3H, 7.26 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ_C 136.2, 135.6, 129.6, 129.4, 128.1, 127.3, 68.8, 31.9, 30.9, 21.9, 13.6.
16. Preparation of **3a**: Compound **2a** (0.24 g, 1.1 mmol) was diluted with 4 mL of a stock solution of 4:1 ethanol/1N H_2SO_4. The biphasic mixture was heated to 50°C forming a homogenous solution which was stirred for 16 h at 50°C. The solution was cooled to room temperature and brine (5 mL) added. The organic layer was separated and concentrated to a yellow oil. The residue was purified by flash chromatography (silica gel, chloroform) to give **3a** as a colorless solid (0.14 g , 83% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 4.28 (s, 2H), 3.72 (s, 2H), 3.08 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 207.4, 132.8, 129.3, 128.9, 127.5, 67.7, 45.8.
17. Many of the alkynes used were commercially available from Aldrich (**1i**, **1h**), Acros (**1g**), Lancaster (**1a**, **1e**), Chemsampco (**1f**), TCI (**1k**), RBI (**1m**) and Maybridge (**1b**, **1c**). The methyl ether (**1l**) was prepared from **1a** by reaction with MeI and NaH. Compound **1j** was prepared by Castro–Stephens coupling of bromobenzene with 3-butyn-1-ol ($PdCl_2$, CuI, PPh_3, and butylamine in MTBE at 50°C). Compound **1d** was prepared by reaction of lithium 4-methoxy-phenylacetylide with formaldehyde in THF.
18. Further optimization of the reaction conditions was performed after the experiments with alkynes **1a**–**1m** with regard to reaction time. The ideal conditions for the preparation of **2b** are as follows: 1-(4-Cyano)-phenyl-1-propyn-3-ol (7.86 g, 50.0 mmol) and 45% KOH (1.28 g, 10.2 mmol) were combined in 50 mL of MeCN at 20°C. *n*-Butanethiol (7.0 mL, 64 mmol) was added via syringe over 30 min with a slight exotherm. After 1 h the crude reaction was concentrated to a dark orange oil. The residue was purified by flash chromatography (silica gel, *t*-BuOMe/hexanes) to provide **2b** as a colorless oil (11.7 g, 95%).
19. Phenylpropiolic acid shows very high reactivity with reaction complete in only 2 h, giving the α product exclusively, as would be expected due to the relatively more electron deficient character of the carboxylic acid.