Pergamon

Tetrahedron Letters, Vol. 36, No. 49, pp. 8917-8920, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01917-0

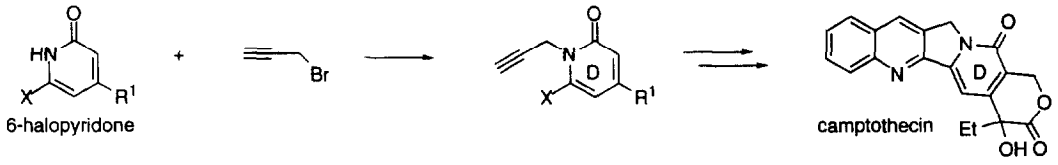
Selective *N*-Functionalization of 6-Substituted-2-Pyridones

Hui Liu, Sung-Bo Ko, Hubert Josien and Dennis P. Curran*
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

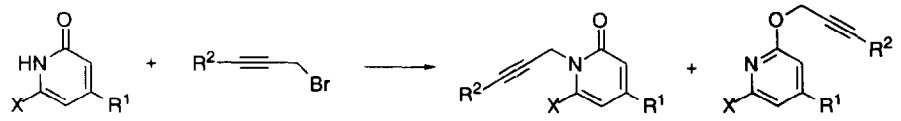
Keywords: 2-pyridone; N-alkylation; N-propargylation

Summary: 6-Substituted-2-pyridones can be selectively *N*-alkylated by treatment with NaH/LiBr in a mixture of DMF and DME. Yields of *N*-propargylated, *N*-allylated, and other *N*-functionalized products are good, and only small amounts of the isomeric *O*-alkylated product (<10%) are typically formed.

The high interest surrounding the camptothecin family of antitumor agents[1] has revived synthetic activity in this area, and several new or significantly improved routes to this class of compounds have recently appeared.[2] A number of these routes pass through *N*-alkyl-2-pyridones. Our strategy, outlined below, calls for an *N*-propargylation of a 6-halopyridone just prior to the key tandem radical reaction.[2f] We have found literature methods inadequate for this *N*-propargylation, and this Letter describes a new procedure that we have developed. This procedure appears to be generally useful for the selective *N*-functionalization of pyridones.



Deprotonation of a pyridone with base provides an ambident anion that can subsequently react on nitrogen or oxygen. The literature records extensive studies on the influence of base, electrophile and solvent on the regioselectivity of *N*- versus *O*-alkylation for the ambident 2-pyridone anion.[3] 6-Substituted-2-pyridones are prone to *O*-alkylation, and typical literature conditions proved unsatisfactory for the selective *N*-propargylation of 6-bromo-2-pyridone (**1a**). We therefore undertook a systematic study with the goal of maximizing the yield of *N*-propargylation.



1a: R^1 = H, X = Br
1b: R^1 = CH_2COOMe, X = Br

2 **3**

Experiments designed to probe the effects of base, solvent, and additive on the *N*-propargylation of **1a** and **1b** are summarized in Table 1. Reaction of the sodium salt of **1a** with propargyl bromide

gave an *N*/*O*-alkylation ratio of 0.38:1 in DMF and 1.3:1 in DME (entries 1, 2). This ratio was nearly unaffected when changing from **1a** to **1b**, reflecting small influence exerted by the R^1 substituent on the regioselectivity (entry 3 vs. 2). Use of methanol as either an additive or solvent slightly increased the ratio **2**:**3** (entries 4, 5, 6). In the case of pure methanol as solvent, 30% starting material remained unreacted. In contrast to the modest solvent effects, the influence of the counteranion was dramatic. When the potassium salt was used instead of the sodium salt, the *O*-alkylated product **3b** was the major product (entry 7), whereas the lithium salt generated from butyllithium gave the *N*-alkylation product **2b** with excellent selectivity (15/1, entry 8). However, the use of butyllithium in hexane is not ideal because the low solvent polarity increased the reaction time and left unreacted starting material.

We thus decided to prepare the lithium salt[4] by treatment of the sodium salt with lithium bromide prior to the addition of propargyl bromide. Small amounts of DMF were also added to increase the solubility of this salt. Under these conditions, **1a** and **1b** were rapidly *N*-propargylated in a ratio only slightly lower than that obtained with n-BuLi (entries 9, 10). However, the isolated yields of **2a** and **2b** from these reactions were moderate (66% and 73%). We then discovered that by increasing the amounts of both DMF and lithium bromide, *N*-propargylation of **1a** occurred in a slighly lower ratio but in a very good isolated yield (86%, entry 11). In terms of yield and selectivity, these conditions are the best that we have found for the 6-substituted-2-pyridone series. By comparison, the procedure recently described by Rico and coworkers for the selective *N*-alkylation of 2-pyridone was not selective when applied to **1a** (entry 12).[5]

Table 1. Propargylation of 6-Bromo-2-pyridones 1 (X = Br; R^2 = H)[a]

Entry	pyridone	Base	Solvent	Additive	Ratio **2**:**3** (Yield **2**, %)
1	**1a**	NaH	DMF	-	0.38 : 1
2	**1a**	NaH	DME	-	1.3 : 1
3	**1b**	NaH	DME	-	1.2 : 1
4	**1b**	NaH	DME	MeOH (1 equiv)	1.3 : 1
5	**1b**	NaH	DME	MeOH (5 equiv)	1.4 : 1
6	**1b**	NaH	MeOH	-	1.8 : 1[b]
7	**1b**	*t*-BuOK	DME	-	0.29 : 1
8	**1b**	*n*-BuLi	DME	-	15 : 1[c]
9	**1a**	NaH	DME	LiBr (1.1 equiv), DMF (1 equiv)	12 : 1 (66)
10	**1b**	NaH	DME	LiBr (1.1 equiv), DMF (1 equiv)	12 : 1 (73)
11	**1a**	NaH	DME/DMF 4 : 1	LiBr (2 equiv)	10 : 1 (86)
12	**1a**	K_2CO_3	$PhCH_3/H_2O$ 100 : 1	*n*-Bu_4NBr	1.5 : 1 (63)

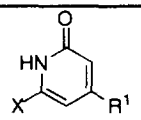
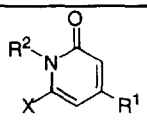
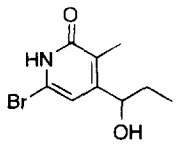
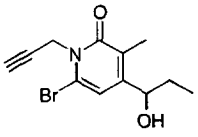
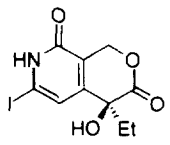
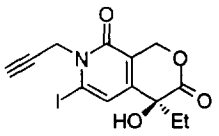
(a) The reaction was carried out with 2 equiv of propargyl bromide. (b) 30% Starting material was recovered. (c) 20% Starting materials remained after 3 days at reflux.

The generality of this procedure has been demonstrated by the reactions of several 6-substituted-2-pyridones with different electrophiles, mainly propargyl derivatives. Table 2 shows selected results. In these experiments, the ratio of *N*/*O*-alkylation was not generally determined, but the high yields of *N*-alkylation products show that *O*-alkylation is a minor pathway (<10%) at best. The chromatographic separation of *N*- and *O*-alkylation products is not difficult.

As evidenced in entries 1 and 2, addition of lithium bromide in the procedure of Rico and coworkers[5] led to *N*-propargylation in good to excellent yield. With our procedure, all *N*-propargyl-

ations occurred smoothly, with yields in the 80-90% range (entries 3-11). Little influence was exerted by either the pyridone substituent or the nature of the propargyl derivative (entries 3 to 7). Similar yields were obtained when allyl bromide (entry 8) or bromoacetonitrile (entry 9) was used as the electrophile. Benzyl and alkyl halides also reacted in good yields, although the *N*/O-alkylation ratio was lower (~5:1). Functionalized pyridones have been used with excellent success (entries 13[6] and 14). The 2-pyridone in entry 13 is an intermediate in the synthesis of mappicine and mappicine ketone,[7] and that in entry 14 is a key precursor of (20*S*)-camptothecin.[8]

Table 2. NaH/LiBr-Mediated *N*-Alkylation of Various 2-Pyridones 1 with Electrophiles[a]

Entry	Pyridone		Alkylating agent	Product
		+	R^2–Hal ⟶	
	X	R^1	R^2	Yield (%)
1	COOMe	H	$HC{\equiv}CCH_2Br$	63[b]
2	CH_2OTHP	H	$HC{\equiv}CCH_2Br$	87[b]
3	Br	H	$HC{\equiv}CCH_2Br$	86
4	I	H	$HC{\equiv}CCH_2Br$	84
5	Br	CH_2COOMe	$TMSC{\equiv}CCH_2Br$	86
6	Br	CH_2COOMe	$PhCH(OTBDPS)C{\equiv}CCH_2Br$	82[c]
7	I	H	$THPOCH_2CH_2C{\equiv}CCH_2Br$	89
8	I	H	$CH_2{=}CH\text{-}CH_2\text{-}Br$	88
9	I	H	$NC\text{-}CH_2\text{-}Br$	87
10	Br	H	$PhCH_2Br$	83[d]
11	Br	H	BuI	71[d]
12	Br	H	EtI	83[d]
13			$HC{\equiv}CCH_2Br$	
				95
14			$HC{\equiv}CCH_2Br$	
				88

(a) See procedure below. (b) Modified Rico procedure, see reference 5. K_2CO_3 (2 equiv)/LiBr (2 equiv)/Bu_4NBr (0.1 equiv), toluene/water 100:1, reflux 1 h. (c) Compared to 63% and 38%, with DMF (1 equiv) and without DMF, respectively. d) For these substrates the use of 4 equiv LiBr in 10:1 DME/DMF gave improved *N/O*-alkylation ratios.

In summary, this procedure holds excellent promise for the selective *N*-alkylation of various functionalized 2-pyridones.

Typical procedure for selective N-alkylation:
To a solution of 2-pyridone (1 mmol) in DME (2.0 mL) and DMF (0.5 mL) under argon was added portionwise 60% NaH (42 mg, 1.05 mmol) at 0 °C. LiBr was added (174 mg, 2 mmol) 10 min later. The mixture was stirred 15 min at room temperature, the electrophile (2 mmol) was added, and the reaction was heated at 65 °C until the TLC analysis showed the absence of starting material (usually 15 h). The mixture was poured into brine (50 mL), extracted with AcOEt (6 x 30 mL), and dried over Na_2SO_4. The residue obtained after concentration of the solvent was purified by flash chromatography over silica gel. Small amounts of the *O*-alkylated product as well as remaining electrophile eluted before the *N*-alkylated product.

Acknowledgment. We are grateful to the National Institutes of Health for support of this research. Financial support for H. J. from Association Francaise pour la Recherche Thérapeutique is gratefully acknowledged.

References and Notes

1. Recent leading references: (a) Camptothecins: New Anticancer Agents (Eds. M. Potmesil, H. Pinedo), CRC Press, Boca Raton, **1995**. (b) Slichenmyer, W. J.; Rowinski, E. K.; Donehower, R. C.; Kaufmann, S.H. *J. Natl. Cancer Inst.*, **1993**, *85*, 271.

2. (a) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971. (b) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331. (c) Fang, F. G.; Xie, S. P.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142. (d) Jew, S. S.; Oh, K. D.; Kim, H. J.; Kim, M. G.; Kim, J. M.; Hah, J. M.; Cho, Y. S. *Tetrahedron: Asymmetry*, **1995**, *6*, 1245. (e) Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611. (f) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863.

3. (a) Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819 and references therein. (b) Diez-Barra, A. E., de la Hoz, A. *Synth. Commun.* **1994**, *24*, 1057. (c) A very recent paper reports alkylation of 2-pyridone with CsF in DMF. Sato, T.; Yoshimatsu, K.; Otera, J. *Synlett* **1995**, 845. Alkylation of **1** with propargyl bromide under these conditions provided **2/3** in a 1/2.6 ratio.

4. Seebach, D.; Beck, A. K.; Studer, A. in "Modern Synthetic Methods", Ernst, B.; Leumann, C., Eds; VCH: Weinhein, 1995, p 1-178.

5. Rico, I.; Halvorsen, K.; Dubrule, C.; Lattes, A. *J. Org. Chem.* **1994**, *59*, 415.

6. When more than 1.05 equiv of NaH was used, the alcohol was also propargylated.

7. Josien, H.; Curran, D. P., manuscript in preparation.

8. Curran, D. P.; Ko, S.-B.; Josien, H. *Ang. Chem., Int. Ed.*, in press.

(*Received in USA* 12 *September* 1995; *revised* 28 *September* 1995; *accepted* 29 *September* 1995)