Tetrahedron Letters 55 (2014) 5591–5594

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest Paper

N-alkylation of lactams with secondary heterobenzylic bromides

Ming Yu *, Karis Stevenson, Gene Zhou

Department of Therapeutic Discovery, Amgen Inc., 1120 Veterans Boulevard, South San Francisco, CA 94080, USA

ARTICLE INFO

Article history:
Received 16 July 2014
Revised 8 August 2014
Accepted 13 August 2014
Available online 19 August 2014

Keywords:
Lactam
N-alkylation
Sodium hydride
Secondary heterobenzylic bromide

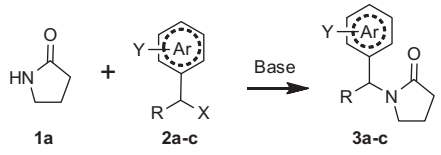
ABSTRACT

We herein report a general N-alkylation reaction of lactams with secondary heterobenzylic bromides. This methodology features mild reaction condition, moderate to high product isolation yield, and broad substrate scope. Good chemical and structural tolerance has also been demonstrated by both the secondary heterobenzylic bromides and lactam substrates.

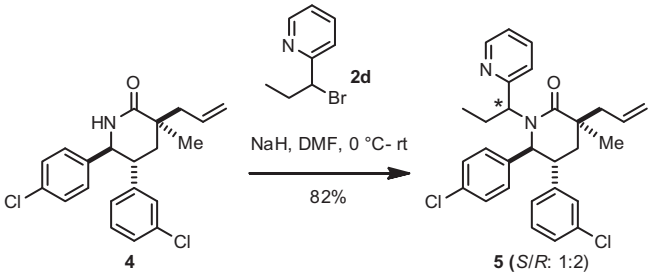
Contents

Introduction

Lactam is a chemical structure frequently encountered in organic chemistry. It is prevalent in naturally occurring products[1] and widely applied in the design and synthesis of bioactive compounds, including β-lactam antibiotics.[2] While N-alkylation of lactams or amides has been well documented with primary benzylic halides **2a** (Ar = Ph; Y = H; R = H; X = Cl, Br, or I, Scheme 1),[3] secondary benzylic halides **2b** (Ar = Ph; R = alkyl; X = Cl, Br, or I), however, are less reported. A successful secondary benzylic halide is usually boosted by an electronic withdrawing group at either the benzylic position (e.g., R = $-CO_2Et$)[4] or the phenyl ring (e.g., Y = 4-fluoro or 3,4,5-trifluoro).[5,6] We postulated that the electronic synergy from these substituents is important for the halides to reach the desired reactivity. Heteroaromatic cycles are generally believed to be more electron deficient than benzene rings (notable exceptions include pyran, thiophene, pyrrole, etc.); therefore the corresponding secondary heterobenzylic halides may be



Scheme 1. N-alkylation of lactams with benzylic halides.



Scheme 2. A recent discovery.

* Corresponding author. Tel.: +1 650 244 2050; fax: +1 650 837 9369.
E-mail address: yum@amgen.com (M. Yu).

http://dx.doi.org/10.1016/j.tetlet.2014.08.060
0040-4039/

considered more reactive than secondary benzylic halides for this reaction. But given the fact that plain secondary benzylic halides (**2c**, Ar = Ph; Y = H; R = alkyl; X = Cl, Br, or I) were reported only sporadically for amide or lactam N-alkylation,[7] the real reactivity of secondary heterobenzylic halides, especially in plain form, is not necessarily certain for this reaction.[8] In this Letter, we report the general observations we made with a large variety of secondary heterobenzylic bromides and lactams for this transformation.

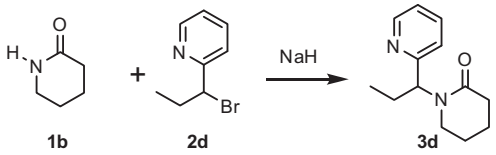
Results and discussions

Our MDM2/P53 inhibitor program recently needed the synthesis of intermediate **5** (Scheme 2). While substrate **4**[9] had been previously N-alkylated with small alkyl halides (e.g., with 2-iodopropane or 3-bromopentane as the solvent in the presence of NaH, 120 °C, 3–6 h, 46–58%),[9–11] reaction of **4** with solid 1-(2-pyridyl)-propyl bromide **2d**, under the compelling steric hindrance from both components, was not necessarily a warranted success. As a matter of fact, the bromide **2d** proved to barely survive harsh reaction conditions. We envisioned that polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF) would benefit this transformation through better solvolysis of the transitional 2-oxopiperidin-1-ide salt upon deprotonation of **4**. Sodium hydride (NaH) could serve as the base for a complete and irreversible deprotonation of **4**, thus driving the reaction to completion. From the first attempt we were pleased to find that the reaction of **4** and **2d** (1.3 equiv) promoted by NaH in DMF at ambient temperature, provided the desired product **5** in 82% isolated yield (a 1:2 mixture of two diastereoisomers).[12] The efficiency observed herein was in contrast to what we previously experienced with many other electrophiles (except α-bromo ester).[9] Encouraged by this result, we set out to study this reaction in general chemical settings to contribute to public chemical community as reference for the scope and limitations of lactam N-alkylation with secondary heterobenzylic bromides.

In experiments designed for reaction condition perfection, piperidin-2-one **1b** was selected as a model substrate for 2-(1-bromopropyl)pyridine **2d** (1.3 equiv) (Table 1). Among the solvents examined, DMF proved to be the most efficient, and facilitated complete consumption of **1b** within one hour at room temperature. Purification of the crude product by flash chromatography on silica gel column provided the desired product **3d** in 85% yield. The reaction was less satisfactory in solvents of decreased polarity (55% and 51% in toluene and THF, respectively), possibly due to weak solvolysis of the intermediate sodium 2-oxopiperidin-1-ide salt. Of note is that there was no O-alkylation product obtained from this reaction. In addition to NaH, other common bases were also screened in an attempt to find a more manageable surrogate. Neither lithium, sodium, or potassium hexamethyldisilazane (LiHMDS, NaHMDS, KHMDS) showed acceptable levels of reaction yield (17%, 28%, and 21%, respectively), although they are usually effective for similar reactions with simple electrophiles. Potassium *tert*-butoxide (KO^tBu) led to poor results (11%), even after prolonged reaction times (15 h) at raised temperatures (100 °C). Cesium and potassium carbonate (Cs_2CO_3 and K_2CO_3) led to very low product yield but recovery of the starting material **1b**.

With reaction conditions finalized, we first investigated the scope of the bromide component. As illustrated in Table 2, a large variety of secondary heterobenzylic bromides were tested for model substrate **1b**. Compared to the 2-pyridylic bromide **2d**, the 3- and 4-pyridylic counterparts (**2e** and **2f**) were equally reactive and resulted in the corresponding products in 84% and 87% yields, respectively. Similar levels of efficiency were also observed with the 2-pyrimidine- and pyrazine-derived bromides (**2g** and **2h**). The secondary benzylic bromide **2i** was less effective but still provided the desired product in 61% yield. As represented by **2j**–**l**, five-membered heterocycles were also investigated for this reaction. Overall a trend of good efficiency was observed across

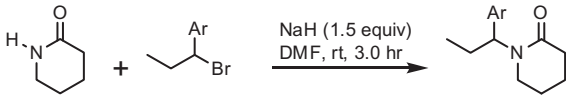
Table 1
Optimization of reaction condition



Entry	Base	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	NaH	DMF	23	1.0	85
2	NaH	Toluene	23	3.0	55
3	NaH	THF	23	4.0	51
4	LiHMDS	DMF	23	2.5	17
5	NaHMDS	DMF	23	4.0	28
6	KHMDS	DMF	23	4.0	21
7	^{t}BuOK	DMF	23	15.0	<5[a]
8	^{t}BuOK	DMF	100	2.0	11
9	Cs_2CO_3	DMF	23	15.0	<3[a]
10	Cs_2CO_3	DMF	100	5.5	<5[a]
11	K_2CO_3	DMF	23	15.0	<3[a]

[a] Yields based on GC–MS analysis of crude reaction mixture.

Table 2
Scope on the aromatic component of bromides



Entry	Heterobenzylic bromide	Ar	Product/yield [a] (%)
1	**2d**		**3d**/85
2	**2e**		**3e**/84
3	**2f**		**3f**/87
4	**2g**		**3g**/83
5	**2h**		**3h**/84
6	**2i**		**3i**/61
7	**2j**		**3j**/88
8	**2k**		**3k**/79
9	**2l**		**3l**/73

[a] Isolated yield.