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Preliminary communication

Reactivity of NBS towards *N*-allyl glycinyl derivatives

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Abstract

The reaction of precursors **3** with NBS in radical conditions does not yield any azetidine resulting from a 4-exo radical cyclisation with bromine atom transfer, or any brominated product at the glycinyl position. Instead, dibrominated adducts **4** and aminals **5** have been formed in good yields. We have investigated the mechanism of this puzzling transformation and shown that the homolytic abstraction of a hydrogen atom by a $Br^{\bullet}$ radical does not take place at the capto-dative position but at the allylic one. The resulting α-bromo derivative **8** would then evolve into an iminium intermediate with concomitant production of bromine and of a succinimidyl anion, which explains the formation of products **4** and **5**. ***To cite this article: C. Koerber et al., C.R. Chimie 6 (2003).***

Résumé

En vue d'accéder à divers composés de type azétidine, nous présentons ici nos résultats sur les possibilités de cyclisation de radicaux glycinyles en conditions de transfert d'atome. En présence de NBS et en conditions de réaction radicalaire, nous obtenons à partir des précurseurs **3**, les produits dibromés **4** et les aminals **5** dans des proportions voisines, mais aucune trace du produit bromé en position glycinyle, ni de l'azétidine résultant de la cyclisation 4-*exo-trig*. Nous avons voulu aller plus loin dans la compréhension de cette réactivité et avons pu démontrer que l'arrachement homolytique d'un atome d'hydrogène par un radical $Br^{\bullet}$ n'a pas lieu en position capto-dative, mais en position allylique. Le produit α-bromé **8** résultant évoluerait ensuite pour engendrer un intermédiaire de type iminium avec production concomitante de dibrome et d'un anion succinimidyle, expliquant la formation des produits **4** et **5**. ***Pour citer cet article : C. Koerber et al., C.R. Chimie 6 (2003).***

Keywords: glycinyl radical; hydrogen abstraction; iminium; allylic amines; *N*-bromo succinimide; α aminoacid

Mots clés : radical glycinyle ; arrachement d'hydrogène ; iminium ; amines allyliques ; *N*-bromo succinimide ; α aminoacide

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1. Introduction

Over the last couple of years, we have been interested in the development of asymmetric radical cyclisation [1, 2]. We have based our approach on the use of sulfoxides as temporary chiral auxiliaries. A sequence involving a radical cyclisation followed by a β-elimination of the sulfinyl moiety could serve in asymmetric intramolecular vinylations to provide enantiopure alkylidene cyclopentanes [3, 4]. We wanted to extend this process to the synthesis of four-membered rings and notably examine the radical cyclisation of a glycinyl radical **1** onto a vinylsulfoxide (Fig. 1). In this case, the sulfinyl group would ensure the diastereoselectivity of the formation of the α-aminoacid stereogenic centre and its rapid β-elimination [5] after cyclisation (radical intermediate **2**) would constitute a sufficient driving force for the construction of this strained structure. This new radical process could find a lot of applications such as the preparation of the polyoximic acid that is the amino-acid core of the natural product polyoxin A [6].

2. Results and discussion

We first examined precursors with no sulfinyl group and incorporating a styryl moiety in order to activate the radical cyclisation step. Moreover, we wished to perform these reactions under atom transfer reactions [7]. The synthesis of glycinyl bromide derivatives is relatively well described in the literature and is generally performed under radical reaction conditions [8, 9].

We therefore submitted precursors of type **3** to the following reagents and conditions: AIBN (10 mol%),

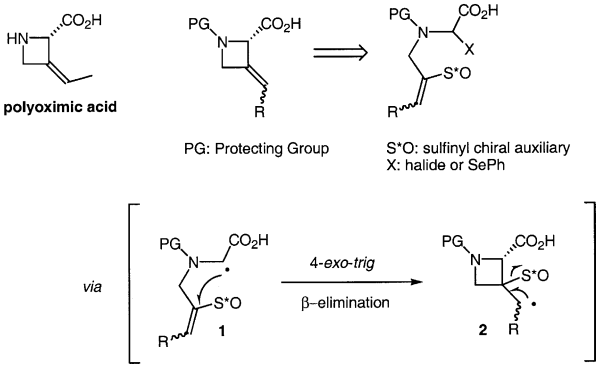

Fig. 1

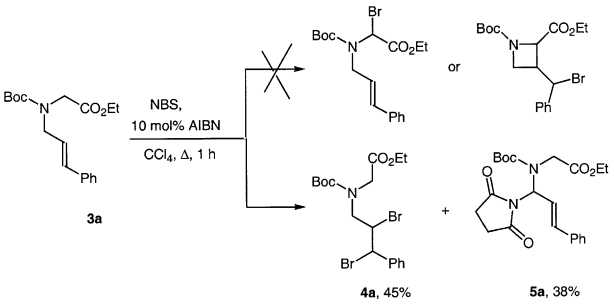

Fig. 2

NBS (1 equiv) in refluxing CCl_4 for 1 h. However, to our surprise, we did not observe any intermediate bromoglycinyl derivative nor the expected azetidine adduct resulting from the radical cyclisation. Instead, we isolated the dibromo derivative **4** and the succinimidyl adduct **5** in good overall yield in a ratio close to 1:1 (Fig. 2).

This rather unexpected turnout of the reaction led us to investigate further substrates to confirm these findings. Since the *N*-alkylation of alkoxycarbonyl-protected glycines gave generally poor yields, the protected group was changed for further studies, and we adopted arylsulfonyl based ones, avoiding tosyl because under radical conditions the benzylic position could be brominated. The synthesis of the precursors was straightforward and is described in Fig. 3. The yields of the *N*-alkylation step are listed in Table 1.

We first concentrated on the behaviour of precursor **3b** that gave the same result and varied the reaction conditions to delineate the optimum conditions for the formation of dibromo derivative **4b** and the succinimidyl adduct **5b** (Fig. 4 and Table 2). It should also be

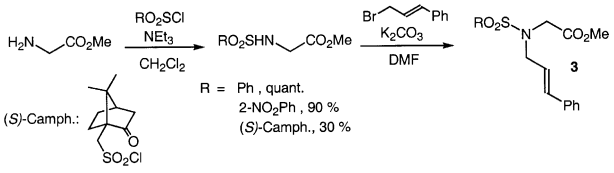

Fig. 3

Table 1
N-alkylation providing precursors **3**.

Entry	R	yield	product
1	Ph	87%	**3b**
2	NO_2–Ph	80%	**3c**
3	Camph	89%	**3d**

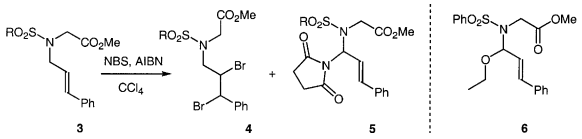

Fig. 4

noted that the structure of aminal **5b** was confirmed by an X-ray analysis.

Some facts can be observed from these experiments. It appears that the starting material always partitions between the two adducts **4b** and **5b** in a close 1:1 ratio. The concentration has no influence on this product distribution (entries 1 & 2). With two equiv. of NBS, one observes the same product distribution (entry 3). The reaction can be induced thermally (AIBN, reflux) or photolytically by a 300-W sunlamp (entries 1 & 4). The reaction is also very efficient in chloroform (entry 5). An interesting finding was that with non-distilled chloroform stabilized with ethanol, adduct **5b** could not be isolated; instead, some other product is observed in 33% yield whose structure was assigned as **6** (entry 6).

In CH_2Cl_2, under thermal conditions (AIBN, reflux), the reaction occurs very slowly because the temperature is probably not sufficient enough to trigger an efficient radical process (entry 7).

The influence of the sulfonyl protecting groups (Table 3) was next examined. In the case of the nosyl group (Ns), two equivalents of NBS were needed for complete consumption of the starting material **3c** (Table 3, entry 1). No diastereoselectivity could be observed when a chiral auxiliary was introduced. Precursor **3d** (Table 3, entry 2) gave an equimolar diastereomeric ratio of adducts **4d** and **5d**.

A question remained to be solved: the functionalization of the obtained adducts **4** and **5** strongly suggests that the aminoacid methylene of the glycine moiety remains intact towards the radical abstraction. To have more evidence on this, we examined the behaviour of the dideuterated precursor **3bD**, easily obtained from **3b** by exchange with NaOEt/DOEt (transesterification also occurred). A mixture of dideuterated adducts **4bD** and **5bD** retaining the deuterium incorporation at the aminoacid site was obtained.

This led us to the mechanism proposal displayed in Fig. 5. After generation of the bromine radical [10], hydrogen abstraction takes place at the allylic position rather than at the glycinyl position, a finding that is consistent with the recent work of Bertrand with thiyl radicals [11]. Comparison of the bond-dissociation energies (BDE), i.e. 81–82 kcal mol^{-1} for allylic amines [12], and 76–83 kcal mol^{-1} for the glycinyl position [13,14,15] does not allow to rationalize this complete chemoselectivity of H-abstraction, but in our case the styryl moiety might bring additional stabilization [16]. Bromination of the intermediate radical **7** would give birth to an α-bromo intermediate **8**, which immediately suffers bromide elimination, producing a highly stabilized iminium species **9** [17, 18], followed by the formation of a succinimidyl anion and bromine. These two new reactants would then respectively add to the iminium intermediate (adduct **5**) and brominate the styryl moiety (adduct **4**).

An alternative pathway could be the oxidation [19] of the α-amino radical 7 with concomitant electron transfer to bromine, which yields the formation of the iminium intermediate **9** and of the bromide anion, and then the same ionic steps operate.

Table 3
Variations of the sulfonyl protecting group.

Entry	conditions	precursor	R	**4**	**5**
1	AIBN, CCl_4, Δ	**3c**	Ns	**4c**, 50%	**5c**, 30%
2	AIBN, CCl_4, Δ	**3d**	Camph	**4d**, 50%	**5d**, 41%

Table 2
Optimisation of the reaction conditions.

Entry	Solvent	Condition	Concentration	Eq. numbers	**3b**	**4b**	**5b**
1	CCl_4	Δ, AIBN	0.05 M	1	—	46%	40%
2	CCl_4	Δ, AIBN	0.02 M	1	—	46%	44%
3	CCl_4	Δ, AIBN	0.05 M	2	—	42%	45%
4	CCl_4	*h ν*, Ar	0.05 M	1	—	40%	38%
5	$CHCl_3$	Δ, AIBN	0.05 M	1	—	50%	50%
6	$CHCl_3$[a]	Δ, AIBN	0.05 M	1.1	—	50%	—[b]
7	CH_2Cl_2	Δ, AIBN	0.05 M	1	62%	22%	16%

Δ = reflux; *hν* = 300-W sun lamp; Ar = bubbling argon through the mixture. [a] Undistilled chloroform stabilized with EtOH. [b] Compound **6** was isolated in 30% yield. [c] Determined by ^1H NMR.

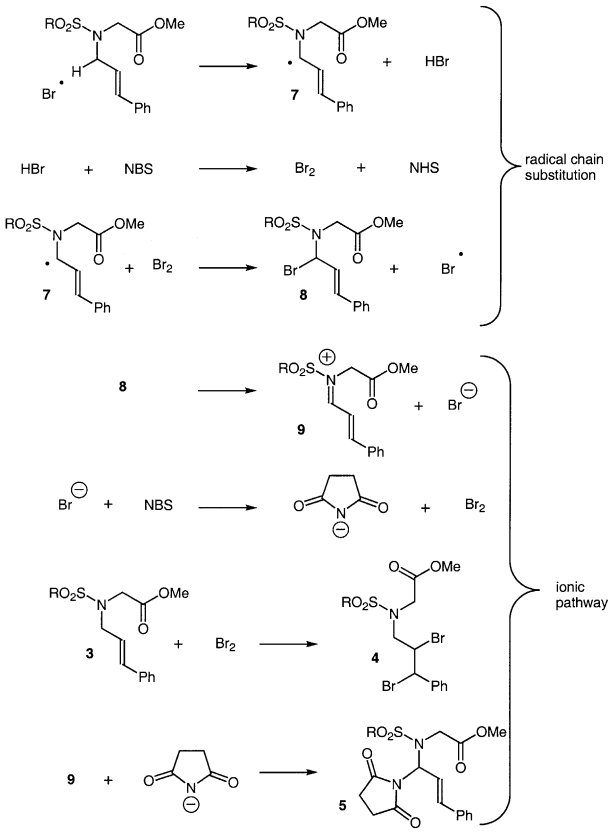

Fig. 5

Finally, an interesting observation was made when a 1:1 mixture of **3b** and **5b** was treated with one equiv of Br_2. After 1 h in refluxing CCl_4, **5b** remained untouched while **3b** was 75% converted to **4b**, showing that bromine, probably for steric reasons, preferably adds to **3b** rather than to the succinimido adduct **5b**.

Naturally, this reaction could take place with a plain alkyl substituted amine **10** leading to brominated and succinimido adducts **11** and **12** in good yields (Fig. 6). Structure of **8** was confirmed by an X-ray analysis.

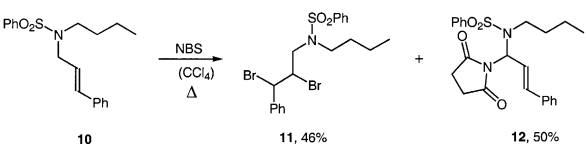

Fig. 6

3. Conclusion

In conclusion, *N*-allyl glycinyl derivatives undergo homolytic hydrogen abstraction at the allylic position and not at the α-aminoacid captodative one. Subsequent formation of an iminium intermediate triggers an ionic path with bromination of the starting material and formation of an aminal adduct. This intermediate can also be trapped with other nucleophiles (alcohols) and we are now directing our efforts towards the design of a clean and efficient *N*-allyl functionalization reaction. These findings augur well for the development of further selective C–H activation reactions, involving the NBS reagent and allowing subsequent polar processes. The system we have studied also represents a mimic of the aerobic oxidation of nitrogen containing substrates by shedding new light on competitive homolytic hydrogen abstractions.

4. Typical experimental procedure

Precursor **3b** (172 mg, 0.5 mmol), NBS (90 mg, 0.5 mmol) and AIBN (6 mg, 0.05 mmol) in 10 ml CCl_4 were refluxed for 1 h. The cold, crude mixture was purified by column chromatography (PE/EA: 60/40 → 0/100) and yielded **4b** in 46% (117 mg) as a colourless oil, which crystallized slowly and **5b** in 40% (90 mg) as colourless oil, which crystallized slowly (recrystallisation from PE/EE).

Dibromo adduct **4b**: m.p.: 99 °C, R_f: 0.54 (PE/EA: 60/40). ^{1}H–NMR ($CDCl_3$, 200 MHz): δ = 3.32 (dd, J = 16.0, 9.5 Hz, 1 H, NC*H*H), 3.47 (s, 3 H, OCH_3), 4.23 (d, J = 18.6 Hz, 1 H, N*H*HCO), 4.39 (d, J = 18.6 Hz, 1 H, NCH*H*CO), 4.51 (dd, J = 16.0, 1.8 Hz, 1 H, NCH*H*), 4.85 (dt, J = 9.5, 1.8Hz, 1 H, BrCH), 4.93 (d, J = 9.5 Hz, 1 H, BrCH), 7.25–7.80 (m, 10 H, arom.). ^{13}C–NMR ($CDCl_3$, 50 MHz): δ = 50.6 (CH_2), 52.1 (OCH_3), 54.2 (BrCH), 54.8 (CH_2), 56.4 (BrCH), 127.6 (CH arom.), 126.9 (CH arom.), 128.5 (CH arom.), 128.7 (CH arom.), 128.9 (CH arom.), 133.0 (CH arom.), 138.4 (C arom.), 139.0 (C arom.), 169.0 (C=O).

Anal. calc. for $C_{18}H_{19}Br_2NO_4S$ (505.22): C, 42.79; H, 3.79; N, 2.77. Found: C, 42.62 ; H, 3.92; N, 2.72.

Aminal **5b**: m.p.: 125.2 °C, R_f: 0.13 (PE/EA: 60/40). ^{1}H–NMR ($CDCl_3$, 200 MHz): δ = 2.49 (s, 4 H, CH_2CH_2), 3.53 (s, 3 H, OCH_3), 4.52 (s, 2 H, CH_2), 6.28 (dd, J = 15.9 Hz, J = 5.6 Hz, 1 H, = CH), 6.43 (d,

J = 15.9 Hz, 1 H, = CH), 6.54 (d, J = 5.6 Hz, 1 H, NCH), 7.22 (s, 5 H, arom.), 7.40–7.95 (m, 5 H, arom.). ^{13}C–NMR ($CDCl_3$, 50 MHz): δ = 27.8 (CH_2CH_2), 47.1 (CH_2), 52.1 (OCH_3), 64.0 (NCH), 119.3 (= CH), 126.7 (CH arom.), 127.8 (CH arom.), 128.5 (CH arom.), 128.7 (CH arom.), 128.8 (CH arom.), 133.1 (CH arom.), 134.8 (C arom.), 135.8 (= CH), 139.2 (C arom.), 170.2 (C = O), 176.2 (NC = O).

Supplementary Material

X-ray data of **5b** and **11** including list of length, angles, ORTEP figures. This supplementary material has been sent to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, and can be obtained by contacting the CCDC (quoting the article details and the corresponding numbers: CCDC 204545 for **5b**, CCDC 204546 for **11**.

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