KOt Bu Promoted Selective Ring-Opening N-alkylation of 2-Oxazolines to Access 2-Aminoethyl Acetates and N-Substituted Thiazolidinones

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Abstract

An efficient and simple KOt Bu promoted selective ring-opening N-alkylation of 2-methyl-2-oxazoline or 2-(methylthio)-4,5-dihydrothiazole with benzyl halides under basic conditions has been described for the first time, which provides a convenient and practical pathway for the synthesis of versatile 2-aminoethyl acetates and N-Substituted thiazolidinones with good functional group tolerance and selectivity. KOt Bu not only plays an important role to promote this ring-opening N-alkylation, but also acts as an oxygen donor.

Keywords

N-Alkylation; Ring Opening; Potassium tert-Butoxide; Thiazolidinones; Oxazolines

Introduction

2-Oxazolines are not only important structure units in pharmaceutical applications and efficient ligands in coordination chemistry, but also valuable protecting or directing groups in catalysis.1-3 2-Oxazolines are a readily stable class of heterocycles resistant against a range of nucleophiles, bases, or radicals,4-5 which could be easily generated from aminoalcohols and carboxylic acids, or from alkenes or epoxides as substrates via alternative synthetic procedures.6 However, under acidic conditions, oxazolines could be transformed to the production of β-substituted carboxamides by nucleophilic ring-opening with SN2 attack at the C5 position of the ring.7-8 Recently, Guo’s group developed an efficient method for the
synthesis of β-nitrate ester carboxamides using tert-butyl nitrite as the nitro source and oxygen as the oxidant through the ring-opening of 2-oxazolines. Kappe reported a two-step continuous flow synthesis of N-(2-aminoethyl)acylamides through ring-opening/hydrogenation of oxazolines with TMSN$_3$ as azide source. Coates described a Co$_2$(CO)$_8$ catalyzed ring-opening hydroformylation of oxazolines to synthesis of β-amidoaldehydes. (Scheme 1) However, the ring-opening N-alkylation of 2-oxazolines to produce 2-aminoethyl acetate derivatives under basic conditions has not been reported.

Thiazolidinone derivatives are important moieties in functional materials and nature products, such as latrunculin obtained from the sponge Cacospongia mycofijiensis. The convenient synthesis of thiazolidinone derivatives has attracted much attention of synthetic chemists. However, only few examples are reported for the synthesis of N-substituted thiazolidinones, even the synthetic method of thiazolidinone was previously described. Recently, Frost and co-workers explored an efficient ruthenium catalyzed O- to S- alkyl migration of N-alkyl oxazolidine-2-thiones to synthesize thiazolidinone derivatives via Barton-McCombie pathway. (Scheme 1)

**Scheme 1.** Comparison of different ring-opening reactions of 2-oxazolines and thiazolidinones synthesis

Recently, potassium tert-butoxide has been shown to be an efficient promoter for the formation of C-C bond. However, only few reports described the C-N bond cross coupling reaction using potassium tert-butoxide as promoter. Wu developed an efficient protocol of
KO’Bu promoted synthesis of 1-aminoisoquinolines from 2-methylbenzonitriles and benzonitriles, and carbonylative cyclization of propargylic amines with selenium under CO gas-free conditions. Based on our continuing interest in developing new transformation methodologies of oxazolines, herein, we report a simple KO’Bu promoted selective ring-opening N-alkylation of 2-methyl-2-oxazolines and 2-(methylthio)-4,5-dihydrothiazole with benzyl halides, leading to 2-aminoethyl acetates and N-substituted thiazolidinone derivatives under mild conditions. (Scheme 1)

Results and Discussion

To test this ring-opening N-alkylation of 2-oxazoline, benzyl bromide (1a) with 2-methyl-2-oxazoline (2) were chosen as the model substrates for the reaction in the presence of 20 mol% of CuBr₂, 2 equiv. of KO’Bu in CH₃CN at 100 °C for 16 h, and full conversion of 2-aminoethyl acetate product 3a was obtained. (Table 1, entry 1) Changed the copper salt to CuBr or CuI, similar results were detected under the same conditions. (Table 1, entries 2 and 3) Surprisingly, when this reaction performed without copper salts and decreasing the temperature to 50 °C in CH₃CN, 99 % GC yield of the desired produce 3a could be still produced. (Table 1, entries 4 and 5). These results showed that copper salt is not necessary for this ring-opening N-alkylation. After several solvents evaluated, such as toluene, EtOH, THF, H₂O, CH₂Cl₂ and DMC (dimethyl carbonate), as DMC is a greener solvent and also give excellent yield of compound 3a, it was shown to be the best solvent for this ring-opening N-alkylation. (Table 1, entry 11) Other potassium salts including KOH, KOAc and PhCOOK could not improve this ring-opening N-alkylation. (Table 1, entries 13-15) However, decreasing the temperature or the amount of KO’Bu to 0.5 equiv led to lower yields. (Table 1, entries 16 and 17) No compound 3a was detected with the absence of KO’Bu, which indicated that KO’Bu plays an important role for promoting this ring-opening N-alkylation. (Table 1, entry 18) Finally, this reaction performed with 1.0 equiv of KO’Bu in DMC at 50 °C for 16 h, was found to be the optimized conditions.

Table 1. Optimization of the KO’Bu promoted selective ring-opening N-alkylation of 2-methyl-2-oxazoline with benzyl bromide.^[a]
| Entry | Catalyst (mol%) | Co-Catalyst (equiv.) | Solvent | Temperature (°C) | GC-yield (%) |
|-------|----------------|---------------------|---------|-----------------|-------------|
| 1     | CuBr₂ (20)    | KO'Bu (2)           | CH₃CN   | 100             | 99          |
| 2     | CuBr (20)     | KO'Bu (2)           | CH₃CN   | 100             | 99          |
| 3     | CuI (20)      | KO'Bu (2)           | CH₃CN   | 100             | 99          |
| 4     | ---            | KO'Bu (2)           | CH₃CN   | 50              | 99          |
| 5     | ---            | KO'Bu (2)           | Toluene | 50              | 58          |
| 6     | ---            | KO'Bu (2)           | EtOH    | 50              | 25          |
| 7     | ---            | KO'Bu (2)           | THF     | 50              | 66          |
| 8     | ---            | KO'Bu (2)           | H₂O     | 50              | ---         |
| 9     | ---            | KO'Bu (2)           | CH₂Cl₂  | 50              | 98          |
| 10    | ---            | KO'Bu (2)           | DMC     | 50              | 98          |
| 11    | ---            | KO'Bu (1)           | DMC     | 50              | 97          |
| 12    | ---            | KO'Bu (0.5)         | DMC     | 50              | 76          |
| 13    | ---            | KOH (1)             | DMC     | 50              | 64          |
| 14    | ---            | KOAc (1)            | DMC     | 50              | 70          |
| 15    | ---            | PhCO₂K (1)          | DMC     | 50              | 48          |
| 16    | ---            | KO'Bu (0.5)         | DMC     | r.t.            | 31          |
| 17    | ---            | KO'Bu (0.5)         | DMC     | r.t.            | ---         |
| 18    | ---            | ---                 | DMC     | 50              | ---         |

[a] KO'Bu, 2-methyl-2-oxazoline (0.5 mmol), benzyl bromide (1.0 mmol), solvent (2 mL), under air for 16 h.

The scope and limitations of this KO'Bu promoted ring-opening N-alkylation from bromide derivatives with 2-methyl-2-oxazolines were then explored using 1.0 equiv of KO'Bu in DMC at 50 °C for 16 h. (Table 1, entry 12) As shown in Scheme 2, various benzyl bromides bearing -Me, -Bu, -F, -Cl groups were applied to the synthesis of tertiary amines 3a-3g in 70-85% yields, respectively. Notably, the steric effect and induce effect did not hamper this ring-opening N-alkylation. Allyl bromide (1h) was successfully reacted with 2-methyl-2-oxazoline and produced corresponding product 3h in good yield. More importantly, bromide containing enoate derivatives 1i and 1j were easily transferred to corresponding ring-opening N-alkylated triesters 3i and 3j containing two C=C bonds, and isolated in 71% and 58% yields.
KO\textsuperscript{t}Bu (0.5 mmol), 2-methyl-2-oxazoline (0.5 mmol), benzyl bromides (1.0 mmol) in DMC (2 mL), at 50 °C, under air for 16 h. **Scheme 2.** KO\textsuperscript{t}Bu promoted selective ring-opening N-alkylation of 2-methyl-2-oxazoline with benzyl bromides.

The above described synthetic system has been evaluated for the ring-opening N-alkylation with benzyl chloride derivatives 2 under similar conditions but at 80 °C, which is expected to be less reactivity than the corresponding benzyl bromides. (**Scheme 3**) Only 26% yield of 2-aminoethyl acetate compound 3a was observed, but the addition of 1.0 equiv of I\textsubscript{2} gave the important role to increase the conversion up to 95% and isolated in 78% yield. Other benzyl chlorides bearing -Me, -Bu, and -F groups at para position were applied to generate corresponding products 3b, 3d, and 3e in moderate to good yields. Furthermore, the reaction could proceed well with heterocycle containing chlorides such as 2-chloro-5-(chloromethyl)thiophene (1k), leading to 2-aminoethyl acetate product 3k in 66% yield which a potential as bifunctional monomer for polymerization.
KO’Bu (0.5 mmol), 2-methyl-2-oxazoline (0.5 mmol), benzyl chlorides (1.0 mmol), I₂ (0.5 mmol) in DMC (2 mL), at 80 °C, under air for 16 h.

Scheme 3. KO’Bu promoted selective ring-opening N-alkylation of 2-methyl-2-oxazoline with benzyl chlorides.

Furthermore, oxazole derivative 2,4,4-trimethyl-4,5-dihydrooxazole was also examined for the KO’Bu promoted ring-opening N-alkylation with 4-methyl benzyl bromide, which successfully led to corresponding compound 3l in 72% isolated yield. (eq 1)

The reaction of 1a with 2-(methylthio)-4,5-dihydrothiazole was performed under similar conditions but with 2 equiv of KO’Bu and 2 equiv. of I₂ at 80 °C. (Scheme 4) However, a N-substituted thiazolidone compound 5a as the only product instead of the above 2-aminoethyl acetate compound was observed in this case. Analogously, the N-substituted thiazolidone derivatives 5a-5h were obtained in 63-90% yields from the corresponding benzyl bromides. The electron donating groups and the electron withdrawing groups did not effect these N-alkylations. Interestingly, the N-alkylation tolerates functional cyano group on aryl ring of benzyl bromide, and the corresponding thiazolidone 5i (80%), was directly obtained without reaction of C≡N bond. The pyridyl and thiophene groups were also applied to the synthesis of the corresponding thiazolidene derivatives in 77% and 50% yields, respectively.
KO\textsubscript{t}Bu (1.0 mmol), 2-(methylthio)-4,5-dihydrothiazole (0.5 mmol), benzyl bromides (1.0 mmol), I\textsubscript{2} (1.0 mmol) in DMC (2 mL), at 80 °C, under air for 16 h.

\textbf{Scheme 3.} KO\textsubscript{t}Bu / I\textsubscript{2} promoted selective N-alkylation to synthesis of thiazolidone derivatives.\textsuperscript{[a]}

On the other hand, further transformation of the 2-aminoethyl acetate product 3a was investigated, and 88% yield of 2-(dibenzylamino)ethanol 6 was successfully produced in the presence of 2.0 equiv of K\textsubscript{2}CO\textsubscript{3} in MeOH at room temperature for 24 h (eq 2). This result indicated that these type of 2-aminoethyl acetate products were useful building blocks for functional alcohols.

\begin{equation}
\text{O-CH}_{2}N_{\text{Ph}} \xrightarrow{K_{2}CO_{3} (2.0 \text{ equiv})} \text{O-CH}_{2}N_{\text{Ph}} \overset{\text{MeOH (2 mL), r.t., 24 h}}{\longrightarrow} \text{N-Ph} \quad (2) \quad 6 \ 88\%
\end{equation}

Next, to gather more information, some control experiments were performed under this ring-opening N-alkylation conditions. First, no conversion of desired product 3a was observed without the addition of KO\textsubscript{t}Bu. However, the addition of 0.2 equiv of KO\textsubscript{t}Bu gave the 2-aminoethyl acetate product 3a in 39% yield under air, and the similar result was obtained under N\textsubscript{2} condition. (eq 3) These results indicated that KO\textsubscript{t}Bu plays an important role to improve the yield of 2-aminoethyl acetate product from this ring-opening N-alkylation. Then, when this reaction is performed in mix-solvent DMC : H\textsubscript{2}O = 8 : 2, only 40% yield of desired
product 3a was produced, while no labelled compound was detected by the $^{18}$O labelled experiment. (eq 4 and 5) These important results revealed that the oxygen of product 3a does not came from water or air, and it may be transferred from KO'Bu, as Dash and co-worker demonstrated KO'Bu could be an oxygen source. In this KO'Bu promoted ring-opening N-alkylation, KO'Bu was not only played an important effect to improve this type of reaction, but also acted a nucleophilic oxygen donor during the C=N bond cleavage process to lead the corresponding 2-aminoethyl acetates.

To gain insight into the reaction mechanism, some control experiments with radical scavenger was performed under the ring-opening N-alkylation conditions. Excellent yield of desired product 3a or 5a was obtained in the presence of the radical scavengers (2, 2, 6, 6-tetra-methylpiperidin-1-yl)oxy (Tempo), Stilbene, or butylated hydroxytoluene (BHT) by the reaction of benzyl bromide with 2-methyl-2-oxazoline or 2-(methylthio)-4,5-dihydrothiazole. (eq 6 and 7) These experimental results suggest that the reaction may proceed through nucleophilic substitution rather than radical pathway.
Conclusion

In summary, we have developed a new and simple transition-metal free promoted selective ring-opening $N$-alkylation of 2-methyl-2-oxazoline or 2-(methylthio)-4,5-dihydrothiazole with benzyl halides and allyl halides under mild conditions. Various 2-aminoethyl acetates and $N$-substituted thiazolidinone derivatives were successfully isolated in moderate to excellent yields. Moreover, in this reaction system, KO'Bu not only plays an important role to promote this ring-opening $N$-alkylation, but also acts as an oxygen donor.

Experimental

General procedure for KO'Bu catalyzed selective ring-opening $N$-alkylation of 2-oxazolines with benzyl bromides
KO'Bu (0.5 mmol, 56 mg), 2-oxazoline (0.5 mmol), benzyl bromide (1.0 mmol) and DMC (2 mL) were introduced in a tube, equipped with magnetic stirring bar and was stirred at 50 °C. After 16 h, the conversion of the reaction was analyzed by gas chromatography. The solvent was then evaporated under vacuum and the desired product was purified by using a silica gel chromatography column and a mixture of petrol ether/ethyl acetate as eluent.

General procedure for KO'Bu catalyzed selective ring-opening $N$-alkylation of 2-oxazolines with benzyl chlorides
KO'Bu (0.5 mmol, 56 mg), I$_2$ (0.5 mmol, 127 mg), 2-oxazoline (0.5 mmol), benzyl chloride (1.0 mmol) and DMC (2 mL) were introduced in a tube, equipped with magnetic stirring bar and was stirred at 80 °C. After 16 h, the conversion of the reaction was analyzed by gas chromatography. The solvent was then evaporated under vacuum and the desired product was
purified by using a silica gel chromatography column and a mixture of petrol ether/ethyl acetate as eluent.

**General procedure for KOtBu / I2 promoted N-alkylation of thiazolidin-2-one derivatives**

KOtBu (1 mmol, 112 mg), I2 (1 mmol, 254 mg), 2-(methylthio)-4,5-dihydrothiazole (0.5 mmol), benzyl halide (1.0 mmol) and DMC (2 mL) were introduced in a tube, equipped with magnetic stirring bar and was stirred at 80 °C. After 16 h, the conversion of the reaction was analyzed by gas chromatography. The solvent was then evaporated under vacuum and the desired product was purified by using a silica gel chromatography column and a mixture of petrol ether/ethyl acetate as eluent.

**Supporting Information**

Supporting information text

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