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KO^{t}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 KO^{t}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. KO^{t}Bu not only plays an important role to promote this ring-opening *N*-alkylation, but also acts as an oxygen donor.

Keywords

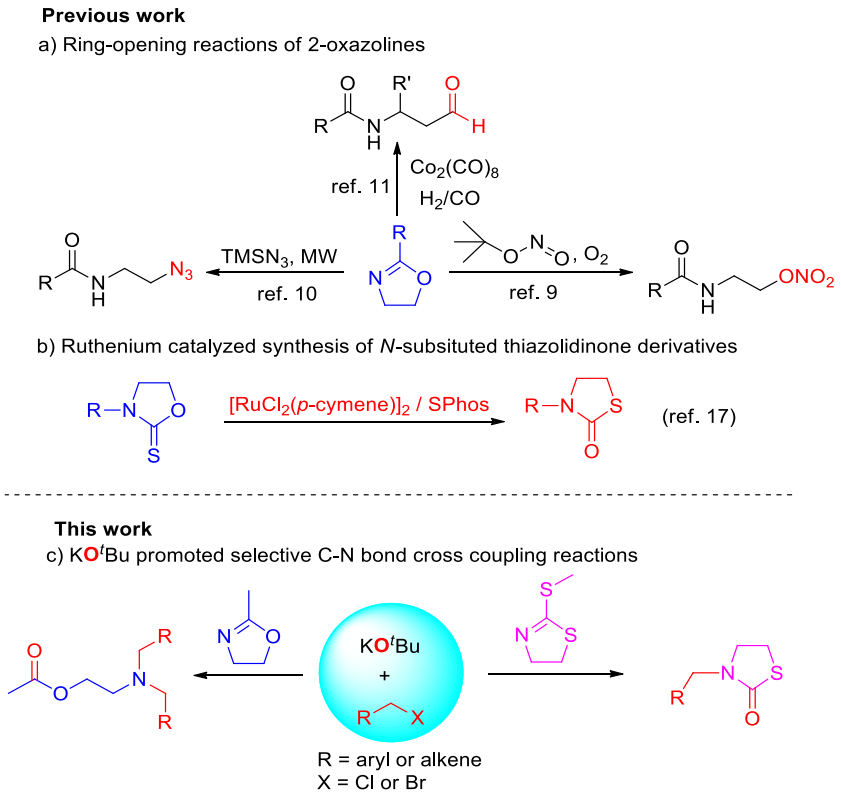
N-Alkylation; Ring Opening; Potassium *tert*-Butoxide; Thiazolidinones; Oxazolines

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 S_N2 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.[9] 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.[10] Coates described a $Co_2(CO)_8$ catalyzed ring-opening hydroformylation of oxazolines to synthesis of *β*-amidoaldehydes.[11] (**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,[12-14] such as *latrunculin* obtained from the sponge *Cacospongia mycofijiensis*.[15] 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.[16] 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.[17] (**Scheme 1**)



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

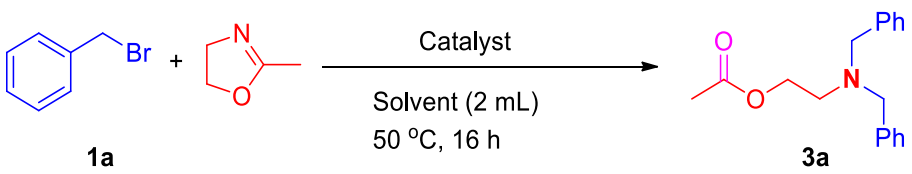
Recently, potassium *tert*-butoxide has been shown to be an efficient promoter for the formation of C-C bond.[18-22] However, only few reports described the C-N bond cross coupling reaction using potassium *tert*-butoxide as promoter. Wu developed an efficient protocol of

KO^{t}Bu promoted synthesis of 1-aminoisoquinolines from 2-methylbenzonitriles and benzonitriles,[23] and carbonylative cyclization of propargylic amines with selenium under CO gas-free conditions.[24] Based on our continuing interest in developing new transformation methodologies of oxazolines,[25] herein, we report a simple KO^{t}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 $CuBr_2$, 2 equiv. of KO^{t}Bu in CH_3CN at 100 ^oC 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 ^oC in CH_3CN, 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, H_2O, CH_2Cl_2 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^{t}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^{t}Bu, which indicated that KO^{t}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^{t}Bu in DMC at 50 ^oC for 16 h, was found to be the optimized conditions.

Table 1. Optimization of the KO^{t}Bu promoted selective ring-opening *N*-alkylation of 2-methyl-2-oxazoline with benzyl bromide.[a]

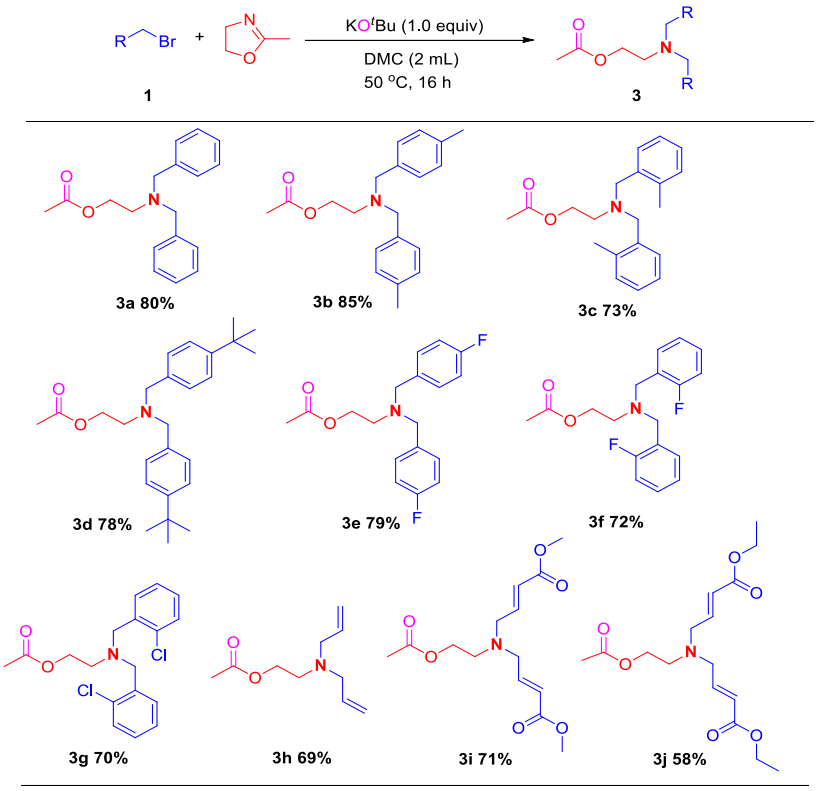


1a **3a**

Entry	Catalyst (mol%)	Co-Catalyst (equiv.)	Solvent	Temperature (°C)	GC-yield (%)
1	$CuBr_2$ (20)	KO^{t}Bu (2)	CH_3CN	100	99
2	CuBr (20)	KO^{t}Bu (2)	CH_3CN	100	99
3	CuI (20)	KO^{t}Bu (2)	CH_3CN	100	99
4	---	KO^{t}Bu (2)	CH_3CN	100	99
5	---	KO^{t}Bu (2)	CH_3CN	50	99
6	---	KO^{t}Bu (2)	Toluene	50	58
7	---	KO^{t}Bu (2)	EtOH	50	25
8	---	KO^{t}Bu (2)	THF	50	66
9	---	KO^{t}Bu (2)	H_2O	50	---
10	---	KO^{t}Bu (2)	CH_2Cl_2	50	98
11	---	KO^{t}Bu (2)	DMC	50	98
12	---	KO^{t}Bu (1)	DMC	50	97
13	---	KOH (1)	DMC	50	76
14	---	KOAc (1)	DMC	50	64
15	---	$PhCO_2K$ (1)	DMC	50	70
16	---	KO^{t}Bu (0.5)	DMC	50	48
17	---	KO^{t}Bu (0.5)	DMC	r.t.	31
18	---	---	DMC	50	---

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

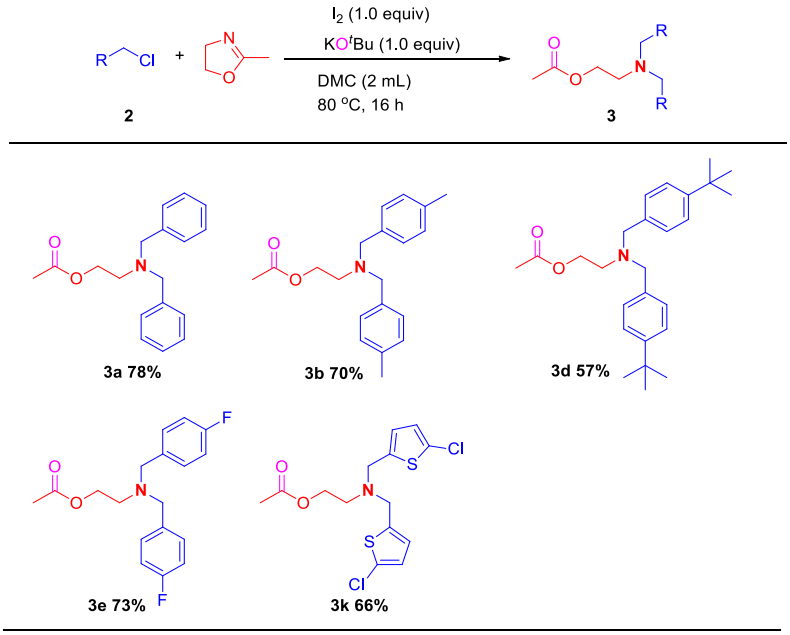
The scope and limitations of this KO^{t}Bu promoted ring-opening *N*-alkylation from bromide derivatives with 2-methyl-2-oxazolines were then explored using 1.0 equiv of KO^{t}Bu in DMC at 50 °C for 16 h. (Table 1, entry 12) As shown in **Scheme 2**, various benzyl bromides bearing -Me, -^{t}Bu, -F, -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^{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^{t}Bu promoted selective ring-opening *N*-alkylation of 2-methyl-2-oxazoline with benzyl bromides.

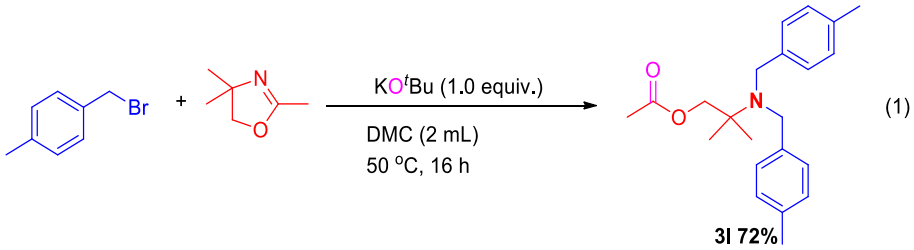
The above described synthetic system has been evaluated for the ring-opening *N*-alkylation with benzyl chloride derivatives **2** under similar conditions but at 80 °C, which is expected to be less reactivity than the corresponding benzyl bromides. (**Scheme 3**) Only 26% yield of 2-aminoethyl acetate compound **3a** was observed, but the addition of 1.0 equiv of I_2 gave the important role to increase the conversion up to 95% and isolated in 78% yield. Other benzyl chlorides bearing -Me, -^{t}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^{t}Bu (0.5 mmol), 2-methyl-2-oxazoline (0.5 mmol), benzyl chlorides (1.0 mmol), I_2 (0.5 mmol) in DMC (2 mL), at 80 °C, under air for 16 h.

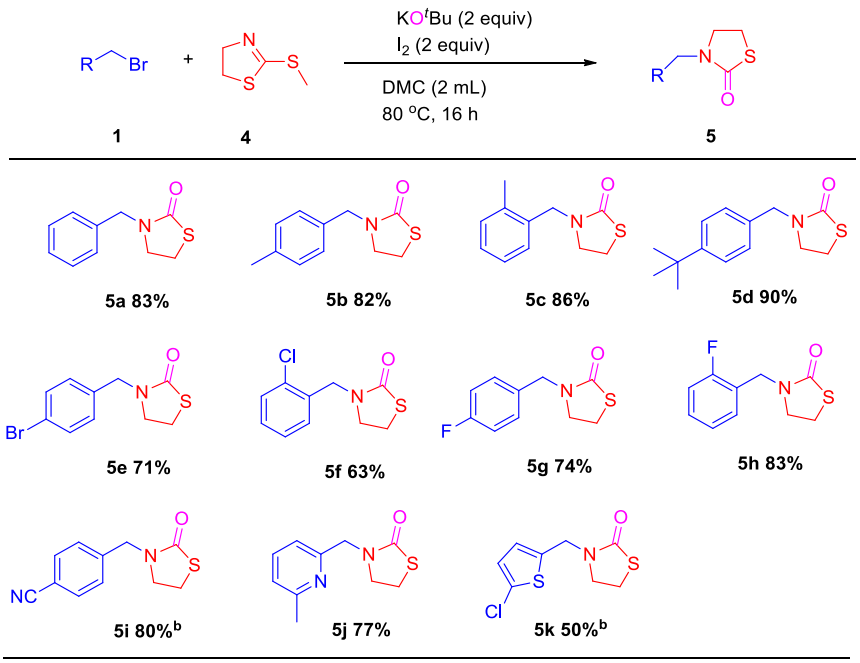
Scheme 3. KO^{t}Bu promoted selective ring-opening *N*-alkylation of 2-methyl-2-oxazoline with benzyl chlorides.

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



(1)

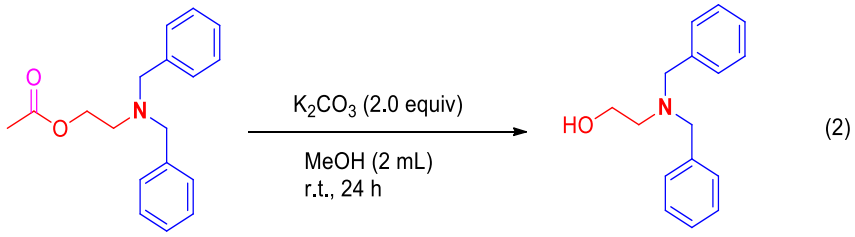
The reaction of **1a** with 2-(methylthio)-4,5-dihydrothiazole was performed under similar conditions but with 2 equiv of KO^{t}Bu and 2 equiv. of I_2 at 80 °C. (Scheme 4) However, a *N*-substituted thiazolidone compound **5a** as the only product instead of the above 2-aminoethyl acetate compound was 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.



[a]KO^{t}Bu (1.0 mmol), 2-(methylthio)-4,5-dihydrothiazole (0.5 mmol), benzyl bromides (1.0 mmol), I_2 (1.0 mmol) in DMC (2 mL), at 80 °C, under air for 16 h. [b]With chloride derivatives.

Scheme 3. KO^{t}Bu / I_2 promoted selective *N*-alkylation to synthesis of thiazolidone derivatives.[a]

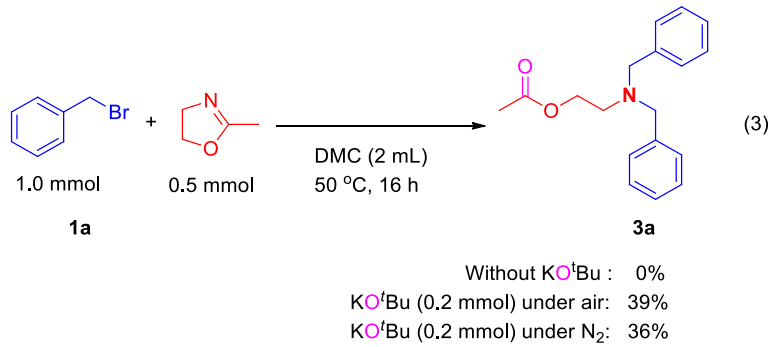
On the other hand, further transformation of the 2-aminoethyl acetate product **3a** was investigated, and 88% yield of 2-(dibenzylamino)ethanol **6** was successfully produced in the presence of 2.0 equiv of K_2CO_3 in MeOH at room temperature for 24 h (eq 2). This result indicated that these type of 2-aminoethyl acetate products were useful building blocks for functional alcohols.

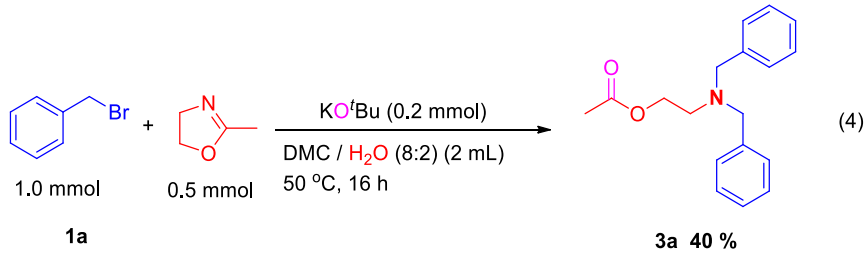


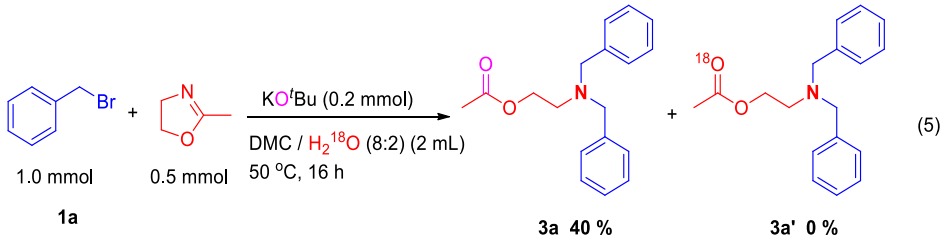
(2)

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^{t}Bu. However, the addition of 0.2 equiv of KO^{t}Bu gave the 2-aminoethyl acetate product **3a** in 39% yield under air, and the similar result was obtained under N_2 condition. (eq 3) These results indicated that KO^{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_2O = 8 : 2, only 40% yield of desired

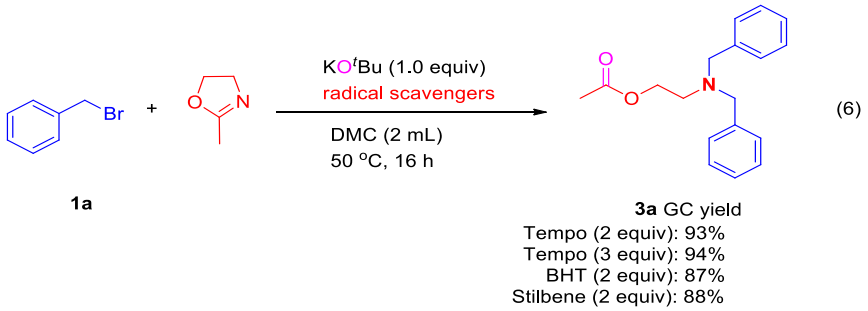
product **3a** was produced, while no labelled compound was detected by the ^{18}O labelled experiment. (eq 4 and 5) These important results revealed that the oxygen of product **3a** does not came from water or air, and it may be transferred from KO^{t}Bu, as Dash and co-worker demonstrated KO^{t}Bu could be an oxygen source.[26] In this KO^{t}Bu promoted ring-opening *N*-alkylation, KO^{t}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.

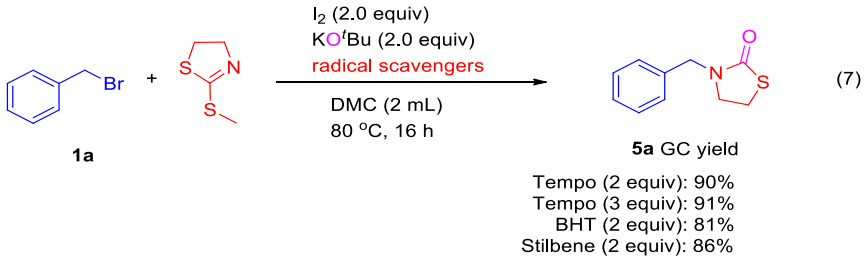






To gain insight into the reaction mechanism, some control experiments with radical scavenger was performed under the ring-opening *N*-alkylation conditions. Excellent yield of desired product **3a** or **5a** was obtained in the presence of the radical scavengers (2, 2, 6, 6-tetra-methylpiperidin-1-yl)oxyl (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^{t}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^{t}Bu catalyzed selective ring-opening *N*-alkylation of 2-oxazolines with benzyl bromides

KO^{t}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^{t}Bu catalyzed selective ring-opening *N*-alkylation of 2-oxazolines with benzyl chlorides

KO^{t}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 KO^{t}Bu / I_2 promoted *N*-alkylation of thiazolidin-2-one derivatives

KO^{t}Bu (1 mmol, 112 mg), I_2 (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 ^{o}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

File Name: Supplementary Information for BJOC

File Format: pdf

Acknowledgements

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