



Fe(II)-catalyzed N-alkylation of sulfonamides with benzylic alcohols

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ARTICLE INFO

Article history:

Received 14 January 2010

Revised 9 February 2010

Accepted 10 February 2010

Available online 13 February 2010

Keywords:

Sulfonamide

Alkylation

Alcohol

Iron

ABSTRACT

The FeCl₂/K₂CO₃ catalyst system was developed successfully for the N-alkylation of sulfonamides with benzylic alcohols via borrowing hydrogen method. XPS analysis suggested a possible catalyst cycle between Fe(II) and Fe(0). Under the optimized condition, the scope of the protocol was demonstrated in 21 different alkylation reactions. High yields, in general >90%, are achieved in most cases.

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The N-alkylated sulfonamide is an important class of compounds in agrochemical and pharmaceutical chemistry.¹ At the same time, sulfonamide could also be used as protecting groups for amine due to the removable sulfonyl group on the nitrogen. Thus, the N-alkylated sulfonamides could also be led to the formation of primary amines.² Typically, the classical methods for the synthesis of N-alkylated sulfonamides are performed by the reaction of sulfonyl halide and amine, sulfonamide and alkyl halide or reductive amination of aldehyde, Scheme 1.³

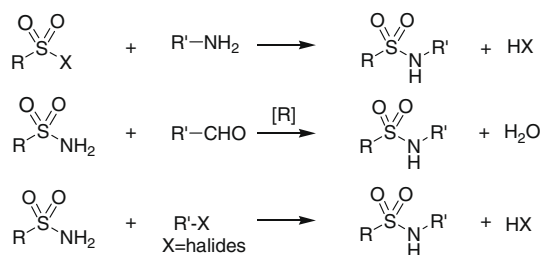
However, all the methods mentioned above suffer from the formation of unexpected byproducts or the application of sensitive substrates. The use of alcohol as alkylation reagent for N-alkylation of sulfonamide is an attractive method because it doesn't generate harmful byproducts and alcohol is readily available.⁴ Some of these reactions have been reported using homogeneous or heterogeneous transition metal catalysts via the so-called borrowing hydrogen methods.⁵ Recently, we have reported a copper-catalyzed N-alkylation of sulfonamides, but the operation of the reaction under air makes the system relatively complicated.⁶ N-Alkylation of sulfonamide and carboxamide have also been realized successfully via a carbocation mechanism using secondary benzylic and allylic alcohols as N-alkylation reagents catalyzed by FeCl₃, MoCl₅ or Bi(OTf)₃.⁷ However, the utilization of Lewis acid causes the difficulty in reaction controlling and product purification. The development of iron catalyzed sulfonamide alkylation method with alcohol through borrowing hydrogen mechanism should be a good choice to solve the above-mentioned problem. Recently, it was

reported that iron could be a good catalyst for the reduction of ketone and amide with additional hydrogen source and elegant results were obtained.⁸ To the best of our knowledge, there is no report about iron-catalyzed sulfonamide alkylation with alcohol through hydrogen-borrowing method.

Herein, we report the Fe(II)Cl₂-catalyzed coupling reaction of sulfonamide and benzylic alcohol via hydrogen-borrowing method, Scheme 2. It was worth noting that a possible cycle between Fe(II) and Fe(0) was observed.

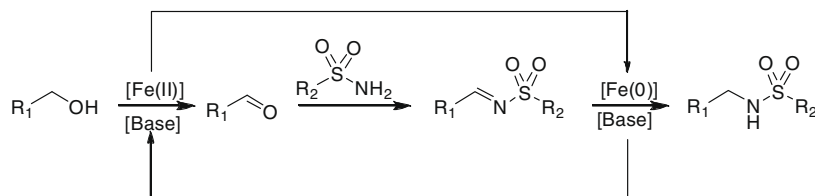
In our initial study, the reaction of *p*-toluene sulfonamide and benzyl alcohol was chosen as the model reaction to explore the catalyst system, Table 1. Generally, the reaction was carried out at 135 °C for 12 h in the presence of a suitable amount of iron salt and 20 mol % base.⁹

By varying different iron salts, that is, FeCl₂, FeCl₃·6H₂O, Fe₃(CO)₁₂, and Fe(acac)₃, we found that FeCl₂ exhibited the highest catalytic activity, Table 1, entries 1–4. The conversion could reach to 90% by simply increasing the FeCl₂ loading to 5 mol %, entry 5.



Scheme 1. Typical protocols for sulfonamide N-alkylation.

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Scheme 2. Iron-catalyzed sulfonamide alkylation with alcohol.

Table 1

The N-alkylation of *p*-toluene sulfonamide with benzyl alcohol^a

Entry	Catalyst	mol %	Base/20 mol %	T (h)	Con. ^b (%)
1	FeCl ₂	1	K ₂ CO ₃	12	40
2	FeCl ₃ ·6H ₂ O	1	K ₂ CO ₃	12	10
3	Fe ₃ (CO) ₁₂	1	K ₂ CO ₃	12	19
4	Fe(acac) ₃	1	K ₂ CO ₃	12	25
5	FeCl ₂	5	K ₂ CO ₃	12	90
6	FeCl ₂	5	KO- <i>t</i> -Bu	12	0
7	FeCl ₂	5	K ₃ PO ₄	12	20
8	FeCl ₂	5	Cs ₂ CO ₃	12	10
9	FeCl ₂	5	K ₂ CO ₃	20	100

^a 2.0 mmol (428 mg) *p*-toluene sulfonamide, 10 mmol (1.08 g) benzyl alcohol, Ar.^b Determined by GC–MS, no other byproduct produced from sulfonamide was observed.

The usage of other bases such as KO-*t*-Bu, K₃PO₄, and Cs₂CO₃ doesn't work better, entries 6–8. There is no observable product if using KO-*t*-Bu as the catalyst. 100% conversion and selectivity could be achieved if prolonging the reaction time to 20 h, entry 9.

In order to explore why FeCl₂ exhibited higher catalytic activity, the reaction system was measured by XPS before and after reaction, Figure 1. The binding energy determined by XPS provides useful information on the oxidation states of different elements.¹⁰ For the fresh sample, the typical bind energy number, that is, 711.6 eV for Fe(II) could be clearly observed. Interestingly, a strong peak at 707.3 eV for Fe(0) could be observed after reaction and there is no evidence for the formation of Fe(III). Therefore, the possible active catalyst species for this coupling reaction is Fe(II) and Fe(0). The transfer hydrogenative process might be realized through the cycle between Fe(II) and Fe(0). At the same time, there is no observable copper element by XPS analysis. So the activity should be originated from iron but not copper pollution although it was reported that copper is the real catalyst in some examples.¹¹ For the XPS analysis of reaction mixture using FeCl₃ as catalyst (not shown here), only Fe(III) could be detected. Thus, both Fe(III) and Fe(II) can promote the reaction but Fe(II) is more active due to the cycle between Fe(II) and Fe(0).

Table 2

The coupling reaction of sulfonamides and benzyl alcohol^a

Entry	RSO ₂ NH ₂	Products	Yield ^b (%)
1			98
2			96
3			93
4			95
5			95
6 ^c			92
7 ^c			90
8 ^c			89

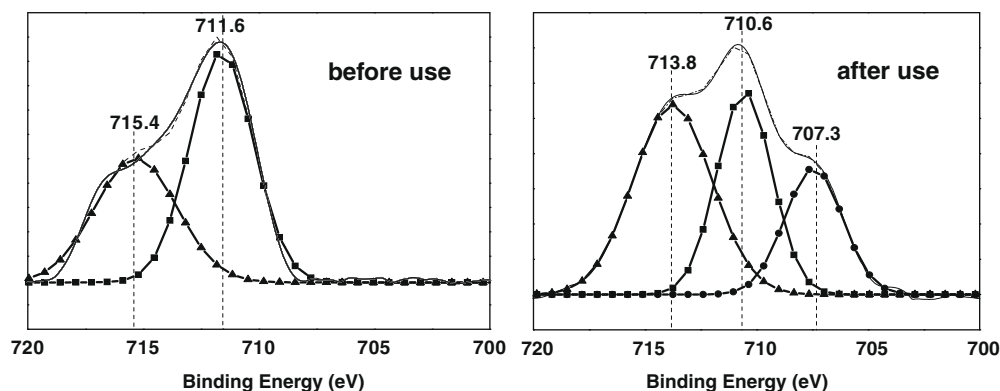
^a Conditions: 1.0 mmol sulfonamides, 5 mmol benzyl alcohols, 5 mol % FeCl₂, 20 mol % K₂CO₃, 20 h, 135 °C, Ar.^b Isolated yield.^c 40 mol % base.

Figure 1. The XPS spectra of the catalyst before and after use.

Table 3
The coupling reaction of *p*-toluene sulfonamide and benzyl alcohol derivatives^a

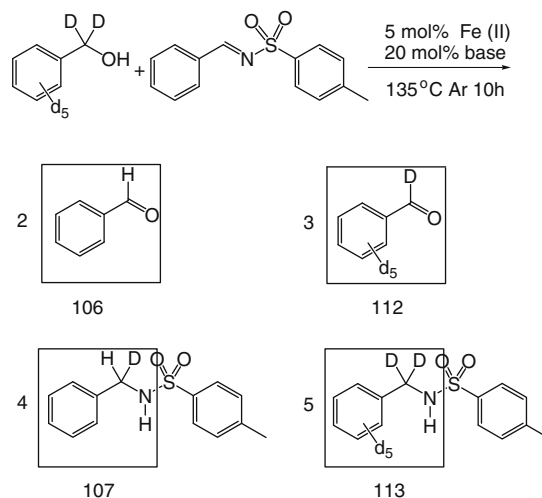
Entry	RCH ₂ OH	Products	Yield ^b (%)
1			89
2			94
3			93
4			92
5			96
6			94
7			95
8			91
9			93
10			92
11			93
12			91
13 ^c			90

^a Conditions: 1.0 mmol sulfonamides, 5 mmol benzyl alcohols, 5 mol % FeCl₂, 20 mol % K₂CO₃, 20 h, 135 °C, Ar.

^b Isolated yield.

^c 40 mol % base.

With a satisfactory protocol in hand, we began to investigate the scope of the reaction of benzylic alcohols and sulfonamides, Table 2. By comparing the N-alkylation reactions of *p*-toluene sulfonamide and 4-bromobenzenesulfonamide with benzyl alcohol, it was clear that electron-rich as well as the electron-poor groups were all tolerant, entries 1–3. For the aliphatic sulfonamide, that is, methyl



Scheme 3. Reaction of benzyl alcohol-*d*₇ with *N*-benzylidene-*p*-toluene sulfonamide.

sulfonamide, 95% isolated yield was also obtained, entry 4. To our delight, if other sulfonamides include naphthalene sulfonamide, thio-phen sulfonamide and pyridine sulfonamide were applied, the yields of the desired products were all ~90%, entries 5–8. These yields were higher than the former reports using iron oxide immobilized nano-ruthenium as catalyst^{5a} and the utilization of noble metal was avoided here.

Nice results were also obtained with the alteration of benzyl alcohols possess different functional groups, Table 3. Under the developed system, all substituted groups, that is, Cl, Br, –CH₃, –CF₃, –OCH₃, –SCH₃, –CH(CH₃)₂, and –CF₃, were stable, and excellent results were achieved. Interestingly, the thiophen-2-ol could also be good alkylation reagent and 90% isolated yield was obtained to the desired product. However, this system is still inactive for the coupling reaction of sulfonamide with aliphatic alcohol. Almost no reaction was observed by applying 1-octanol as starting material.

The mechanism was explored by the reaction of benzyl alcohol-*d*₇ with *p*-toluene sulfonamide or *N*-benzylidene-*p*-toluene sulfonamide. By tracing the reactions with GC–MS, it showed that the formation of products **2**, **3**, **4**, and **5**, Scheme 3, which proved the transfer hydrogenative mechanism and also the whole process was reversible. Isotope effect investigation suggested that the KIE₁ was 3.6, which provided strong evidence that the hydrogen elimination was the rate-determining step.¹²

In conclusion, a new FeCl₂/K₂CO₃ catalyst was developed for the environmentally benign N-alkylation of sulfonamide with benzylic alcohol. The underlying C–N bond formation reaction takes place with high selectivity giving only water as side product. Generally, isolated yields higher than 90% were achieved. XPS analysis suggested a possible catalyst cycle between Fe(II) and Fe(0).

Acknowledgment

This work was financially supported by the ‘Hundred Talents Program’ of the Chinese Academy of Sciences.

Supplementary data

Supplementary data (procedure for the reaction and ¹H NMR results for the products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.056.

References and notes

- (a) Cole, D. C.; Lennox, W. J.; Lombardi, S.; Ellingboe, J. W.; Bernotas, R. C.; Tawa, G. J.; Mazandarani, H.; Smith, D. L.; Zhang, G.; Coupet, J.; Schechter, L. E. *J. Med. Chem.* **2005**, *48*, 353; (b) Koehle, N. K. U. *J. Med. Chem.* **2004**, *47*, 4989.
- Quaal, K. S.; Ji, S.; Kim, Y. M.; Closson, W. D.; Zubieta, J. A. *J. Org. Chem.* **1978**, *43*, 1311.
- (a) Caddick, S.; Wilden, J. D.; Wadman, S. J.; Bush, H. D.; Judd, D. B. *Org. Lett.* **2002**, *4*, 2549; (b) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725; (c) Caddick, S.; Wilden, J. D.; Judd, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 1024.
- (a) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555; (b) Kim, J. W.; Yamaguchi, K.; Mizuno, N. *J. Catal.* **2009**, *263*, 205; (c) Lamb, G. W.; Williams, J. M. J. *Chim. Oggi.* **2008**, *26*, 17; (d) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358.
- (a) Shi, F.; Tse, M. K.; Zhou, S.; Pohl, M. M.; Radnik, J.; Huebner, S.; Jaehnisch, K.; Bruecker, A.; Beller, M. *J. Am. Chem. Soc.* **2009**, *131*, 1775; (b) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766; (c) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.
- (a) Shi, F.; Tse, M. K.; Cui, X.; Gördes, D.; Michalik, D.; Thurow, K.; Deng, Y.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5912; (b) Cui, X.; Shi, F.; Tse, M. K.; Gördes, D.; Thurow, K.; Beller, M.; Deng, Y. *Adv. Synth. Catal.* **2009**, *351*, 2949.
- (a) Qin, H.; Yamagiwa, N.; Matsunga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409; (b) Sreedhar, B.; Reddy, P. S.; Reddy, M. A.; Neelima, B.; Arundhathi, R. *Tetrahedron Lett.* **2007**, *48*, 8174; (c) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858; (d) Reddy, C. R.; Madhavi, P. P.; Reddy, A. S. *Tetrahedron Lett.* **2007**, *48*, 7169.
- (a) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9507; (b) Shaikh, N. S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2497.
- General procedure for N-alkylation reactions:* Typically, 1.0 mmol *p*-toluenesulfonamide (171 mg), 5.0 mmol benzyl alcohol (540 mg), 5 mol% FeCl₂ (10 mg) catalyst and 20 mol% K₂CO₃ (69 mg) were added to the reaction tube, respectively. Then, the reaction was carried out applying a multi-reactor (Carousel 12 station, RADLEYS) at 135 °C for 20 h. Then it was cooled to room temperature. ~20 mL acetone was added to dissolve the reaction mixture and filtered by Celite. The acetone and benzyl alcohol were removed under vacuum and a white solid was obtained with 98% isolated yield. ¹H NMR (400.1 MHz, CDCl₃): δ = 2.44 (s, 3H), 4.05–4.15 (d, 2H), 4.80–4.90 (t, 1H), 7.13–7.36 (m, 7H), 7.70–7.79 (d, 2H), ¹³C NMR (100.6 MHz, CDCl₃): δ = 21.50, 47.20, 127.14, 127.84, 128.64, 129.70, 136.23, 136.79, 143.49; MS (E.I., 70 eV) *m/z* (rel. int.) 261 (1), 155 (5), 139 (6), 107 (10), 106 (100), 104 (9), 92 (21), 91 (59), 89 (6), 79 (15), 78 (7), 77 (20), 63 (5), 51 (10), 39 (8), 28 (10).
- Kirumakki, S. R.; Shpeizer, B. G.; Sagar, G. V.; Chary, K. V. R.; Clearfield, A. J. *Catal.* **2006**, *242*, 319.
- Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.
- (a) Banerji, K. K. *J. Chem. Soc., Perkin Trans.* **1973**, *2*, 435; (b) Che, C. M.; Tang, W. T.; Lee, W. O.; Wong, K. Y.; Lau, T. C. *Dalton Trans.* **1992**, 1551; (c) Oh, N. Y.; Suh, Y.; Park, M. J.; Seo, M. S.; Kim, J.; Nam, W. *Angew. Chem., Int. Ed.* **2005**, *44*, 4235; (d) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.