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Microwave-assisted oxidative coupling of amines to imines on solid acid catalysts

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Abstract—A K-10 montmorillonite catalyzed microwave-assisted oxidative coupling of amines is described. Substituted benzylamines readily undergo self-coupling reactions to produce benzylidene–benzylamines, while aliphatic amines and anilines cannot form self-coupled products. A mixture of a benzylamine and an aniline or aliphatic amine, respectively, effectively, and selectively produces mixed imines, such as benzylidene–anilines and benzylidene–alkylamines.
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1. Introduction

Chiral amines are important intermediates in the synthesis of biologically active compounds.[1] As imines are versatile starting materials for chiral amine synthesis,[2] their preparation attracts extensive attention. The traditional condensation reaction of carbonyl compounds with primary amines is a well-studied reaction.[3] However, the direct oxidative coupling of amines to imines without the use of any carbonyl compound can serve as a novel alternative.[4]

Most of these sporadic oxidation processes utilize stoichiometric reagents with strong emphasis on nitrile and hydroxylamine synthesis.[5] Stoichiometric processes for the oxidation of amines to imines are also available.[6] Due to recent environmental considerations, strengthening safety concerns, and economic views, however, the use of such reagents is undesirable. As a result, extended efforts have been made to develop catalytic systems that utilize inorganic or organic peroxides, hydroperoxides as oxidants.[7] The use of heteropoly-oxometallates involves molecular oxygen as oxidative agent in a catalytic process, however, the catalyst recycling raises problems.[8] Similar difficulties occur with polyaniline-based oxidation catalysts.[9] Recently, details on the effective

heterogeneous catalytic synthesis of nitriles on supported metal catalysts and on using molecular oxygen have been published.[10] Although many suggestions have been made to interpret the mechanism of these oxidations, it is still controversial. Extended theoretical studies were also carried out to clarify the mechanistic explanation.[11]

Over the past two decades, microwave-assisted organic synthesis has emerged as an important area.[12] It is a convenient and time saving method, which promotes the application of environmentally benign approaches such as solvent-free and heterogeneous catalytic reaction conditions.[13]

Here, we report a new effective heterogeneous catalytic oxidative coupling of amines catalyzed by a solid acid, K-10 montmorillonite to yield a wide variety of imines. The major advantages of the process are the use of a readily available and economic catalyst, the solvent-free system and the short reaction times.

Recently, we have observed the formation of a considerable amount of benzylidene–benzylamine from benzylamine in the presence of solid acid catalysts. This prompted us to study the self-coupling reaction of benzylamine on several solid acid catalysts (Scheme 1).

Weak acids (silica, alumina) provided low yield (∼10%) or no product formation. In contrast, activated carbon

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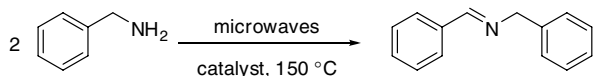
Scheme 1. Oxidative self coupling of benzylamine in the presence of solid catalysts.

support yielded benzaldehyde selectively in 98%, but no formation of benzylidene–benzylamine was observed. Solid superacidic perfluorinated resinsulfonic acid Nafion-H[14] gave moderate yields (∼15%), with the formation of significant amount of byproducts. Finally, it was found that the best catalyst for the reaction is K-10 montmorillonite (K-10). It is a strong solid acid[15] and also used in bifunctional catalysis.[16] K-10 is prepared from natural montmorillonite by mineral acid treatment.[17] Its main constituent is a quartz-like material, in addition to kaolinite and montmorillonite.[18] Its Hammett acidity ($H_0 = -8$) is similar to that of concd nitric acid.[15] Besides its BET surface exceeds $250 \, m^2 \, g^{-1}$.[15] Although originally we observed the coupling reaction using traditional conductive heating (external oil bath), the application of microwave irradiation significantly increased the reaction rates and yields (3 min compared to 24 h). First we investigated the self-coupling of substituted benzylamines (Table 1).[19]

As the data show, the corresponding substituted benzylidene–benzylamines formed in good to excellent yields in very short reaction times. Further irradiation results in the formation of significant amount (up to 20%) of symmetric N,N-dibenzylamines. The formation of these saturated products can be explained by extended disproportionation providing a suitable hydrogen source for transfer ionic hydrogenation of the benzylidene products.[20] The self-coupling reaction is characteristic for benzylamines, aliphatic amines provided the expected Schiff-bases only in minor amount. Other amines with no α-hydrogen, such as anilines, do not undergo self-coupling reactions.

Although anilines cannot undergo self-coupling, they readily react with benzylamines to form N-benzyl-

Table 1. Microwave-assisted oxidative self-coupling of substituted benzylamines on K-10 montmorillonite[a]

Entry	R	Time (min)	Yield[b] (%)
1	H	3	80
2	p-CH$_3$	3	88
3	m-CH$_3$	1	80
4	o-F	1	86
5	p-F	1	98
6	p-Cl	2	96
7	m-CF$_3$	6	76
8	o-OCH$_3$	2	87[c]

[a] Reaction conditions: benzylamine (1.0–4.6 mmol), 1 g catalyst, 150 °C, 1 bar air.
[b] Based on benzylamine, determined by GC and GC–MS.
[c] At 140 °C.

idene–anilines under the general experimental conditions.[19] Representative examples are shown in Table 2.

The reaction can be carried out effectively with a wide variety of benzylamines and anilines. The optimization of reaction conditions resulted in good to excellent yields. In the case of prolonged reaction times, the formation of the saturated product can also be observed in minor amounts (usually less than 5%). When the reaction is not complete, the major byproduct is always the substituted benzylidene–benzylamine. This suggests that in the first step benzylamine undergoes self-coupling, and forms benzylidene–benzylamine. Aniline most likely reacts with this product.

As mentioned, aliphatic amines formed self-coupled Schiff-bases only in low yields. However, they readily react with benzylamines (Table 3).

As the data show, the reactions are relatively slow and the yields are moderate. It appears that steric effects play little role in these reactions, cyclic amines react similarly
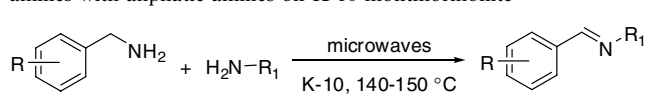
Table 2. Microwave-assisted oxidative coupling of substituted benzylamines with anilines on K-10 montmorillonite[a]
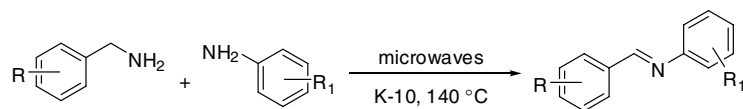
Entry	R	R$_1$	Time (min)	Yield[b] (%)
1	H	p-F	18	90
2	H	m-CF$_3$	33	79
3	p-CH$_3$	H	45	84
4	p-CH$_3$	p-F	21	83
5	m-CH$_3$	H	35	85
6	m-CH$_3$	p-F	18	93
7	o-OCH$_3$	p-F	30	78
8	p-F	p-F	23	81
9	p-Cl	p-F	18	86
10	m-CF$_3$	p-F	18	98
11	m-CF$_3$	m-CF$_3$	28	79

[a] Reaction conditions: benzylamine (2.75 mmol), aniline (2.75 mmol), 1 g catalyst, 100 °C, 1 bar air.
[b] Based on aniline, determined by GC and GC–MS.

Table 3. Microwave-assisted oxidative coupling of substituted benzyl-amines with aliphatic amines on K-10 montmorillonite[a]

Entry	R	R_1	Time (min)	Yield[b] (%)
1	H	Cyclopentyl[c]	19	72
2	H	n-Hexyl[d]	30	50
3	p-CH$_3$	Cyclopentyl[c]	60	34
4	p-CH$_3$	n-Hexyl[d]	30	28
5	p-F	Cyclopentyl[c]	21	64
6	p-F	n-Hexyl[d]	40	34
7	p-Cl	n-Hexyl[d]	20	28
8	p-Cl	Cyclopentyl[c]	30	33

[a] Reaction conditions: benzylamine (2.75 mmol), alkylamine (5.5 mmol), 1 g catalyst, 100 °C, 1 bar air; after half reaction time extra 0.5 equiv alkylamine was added.
[b] Based on alkylamine, determined by GC and GC–MS.
[c] 140 °C.
[d] 150 °C.

to open chain analogs. Further increase in reaction times resulted in a significant amount of byproducts.

It is worth noting that to carry out coupling reaction with two different benzylamines, experiments provided a mixture of all possible products. As a major direction of the reaction, the two different benzylamines underwent self-coupling and did not provide the mixed Schiff-bases in good yield or selectivity.

Although it is premature to provide a complete mechanistic interpretation, based on earlier literature data[8,11] and our own observations, the most likely pathway of the reaction is as follows. The acidic centers of K-10 coordinate the non-bonded electron pair of nitrogen and make it sensitive to oxidation. One important question is how the initial step occurs. Earlier literature reports speculate on the formation of an N-oxide and then its transformation to benzaldehyde that can react with the remaining benzylamine.[8,11] Our recent results on K-10 catalyzed synthesis of pyrazole derivatives, however, suggest a different pathway. We have observed that K-10 montmorillonite readily dehydrogenates pyrazolines to pyrazoles in good yields.[21] As K-10 does not have traditional oxidative active centers, we propose a dehydrogenative pathway for the formation of an intermediate imine. This imine then undergoes a trans-amination[22] with a second, yet unreacted benzylamine to form benzylidene–benzylamine (Scheme 2.)

A similar mechanism can be applied for the formation of mixed imines (benzylidene–anilines or benzylidene–alkylamines) with a minor addition. Kinetic studies on the benzylamine–aniline reaction revealed that benzyl-amine undergoes a rapid self-coupling and disappears from the reaction mixture with the parallel appearance of benzylidene–benzylamine. The benzylidene–benzyl-amine concentration increases until benzylamine is completely consumed by the reaction. In parallel, the gradual increase of the benzylidene–aniline can be observed. As a result, the benzylidene–benzylamine
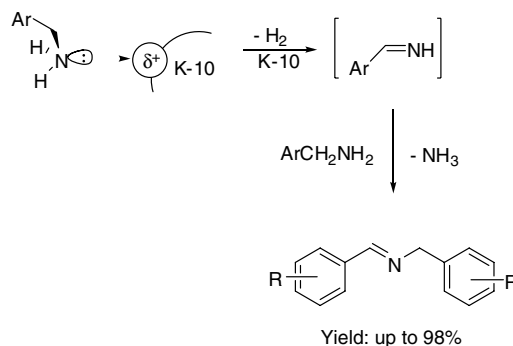
Scheme 2. Proposed scheme for the oxidative self-coupling of benzyl-amines in the presence of K-10 montmorillonite.
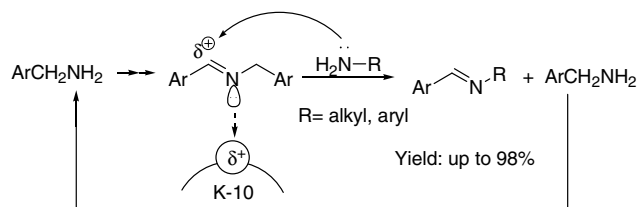
Scheme 3. Proposed scheme for the reaction of benzylamine with substituted anilines or aliphatic amines in the presence of K-10 montmorillonite.

concentration shows a maximum curve. It indicates that the benzylidene–benzylamine serves as an intermediate in reactions with another amine, such as aniline and its derivatives. After benzylamine is completely reacted, aniline will undergo transamination with benzylidene–benzylamine. Although the kinetic data provide a clear picture, we have made an effort to support this kinetic hypothesis. In an independent reaction, benzylidene–benzylamine (synthesized prior to this reaction) was reacted with aniline. As observed, the product benzyl-idene–aniline formed in 98% yield providing support for the two-step mechanism. The observations are summarized in Scheme 3.

In conclusion, the oxidative coupling of benzylamines with a wide variety of amines produces the corresponding self-coupled or mixed Schiff-bases. As the reaction is catalyzed by K-10 montmorillonite, a versatile solid acid catalyst, and carried out without solvent it provides an environmentally benign process for the alternative synthesis of such imines.

References and notes

1. For example see: Bishop, M. J.; McNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311; Sakurai, S.; Ogawa, N.;

Suzuki, T.; Kato, K.; Ohashi, T.; Yasuda, S.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1996**, *44*, 765; Hermanns, D.; Bolm, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692.

2. Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895; Block, R. *Chem. Rev.* **1998**, *98*, 1407; Kobayashi, S.; Ishitami, H. *Chem. Rev.* **1999**, *99*, 1069; Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 924; Pugin, B.; Landert, H.; Spindler, F.; Blaser, H.-U. *Adv. Synth. Catal.* **2002**, *344*, 974; Török, B.; Prakash, G. K. S. *Adv. Synth. Catal.* **2003**, *345*, 165.

3. Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039; Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463; Abid, M.; Savolainen, M.; Landge, S.; Hu, J.; Prakash, G. K. S.; Olah, G. A.; Török, B. *J. Fluorine Chem.* **2007**, *128*, 587.

4. Sheldon, R. A.; Kochi, J. K. Metal Catalyzed Oxidations of Organic Compounds; Academic Press: New York, 1981; Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monographs Series; ACS: Washington, DC, 1990.

5. George, M. V.; Balachandran, K. S. *Chem. Rev.* **1975**, *75*, 491; Capedeville, P.; Lavigne, A. *Synthesis* **1989**, 453.

6. Orito, K.; Hatakeyama, T.; Takeo, M.; Uchiito, S.; Tokuda, M.; Suginome, H. *Tetrahedron* **1998**, *54*, 8403; Doctorovich, F.; Trapani, C. *Tetrahedron Lett.* **1999**, *40*, 4635.

7. Sheldon, R. A. *Green Chem.* **2000**, *2*, G1; Anastas, P. T.; Bartlett, L. B.; Kirchoff, M. M.; Williamson, T. C. *Catal. Today* **2000**, *55*, 11; Suresh, S.; Joseph, R.; Jayachandran, B.; Pol, A. V.; Vinod, A. V.; Sudalai, A.; Sonawane, H. R.; Ravindranathan, T. *Tetrahedron* **1995**, *51*, 11305.

8. Nakayama, K.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Chem. Lett.* **1993**, 1699; Neumann, R.; Levin, M. *J. Org. Chem.* **1991**, *56*, 5707.

9. Hirao, T.; Higuchi, M.; Ikeda, I.; Oshiro, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 194; Higuchi, M.; Ikeda, I.; Hirao, T. *J. Org. Chem.* **1997**, *62*, 1072.

10. Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2001**, 461; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *8*, 1049.

11. Thiel, W. R.; Khron, K. *Chem. Eur. J.* **2002**, *8*, 1049.

12. Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2002; Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005; Tierney, J. P.; Lidstrom, P. *Microwave Assisted Organic Synthesis*; Blackwell: Oxford, 2005.

13. Varma, R. S.; Naicker, K. P.; Kumar, D.; Dahiya, R.; Liesen, P. J. *J. Microwave Power Electromagn. Energy* **1999**, *34*, 113; Ahn, J. A.; Chang, D. H.; Park, Y. J.; Yon, Y. R.; Loupy, A.; Jun, C. H. *Adv. Synth. Catal.* **2006**, *348*, 55; Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I. J.; Chang, D. H.; Jun, C. H. *Tetrahedron* **2004**, *60*, 5539; Rodriguez, H.; Suarez, M.; Perez, R.; Petit, A.; Loupy, A.

Tetrahedron Lett. **2003**, *44*, 3709; Miyazawa, A.; Tanaka, K.; Sakakura, T.; Tashiro, M.; Tashiro, H.; Prakash, G. K. S.; Olah, G. A. *Chem. Commun.* **2005**, 2104; Ju, Y. H.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135; Abid, M.; Landge, S. M.; Török, B. *Org. Prep. Proceed. Int.* **2006**, *35*, 495; Abid, M.; Spaeth, A.; Török, B. *Adv. Synth. Catal.* **2006**, *348*, 2191.

14. Olah, G. A.; Iyer, P. S.; Prakash, G. K. S. *Synthesis* **1986**, 513; Pálinkó, I.; Török, B.; Prakash, G. K. S.; Olah, G. A. *Appl. Catal., A* **1998**, *174*, 147; Török, B.; Kiricsi, I.; Molnár, Á.; Olah, G. A. *J. Catal.* **2000**, *193*, 132.

15. Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays*; Springer: Berlin, 1993; Srinivas, K. V. N. S.; Das, B. *J. Org. Chem.* **2003**, *68*, 1165; Abid, M.; Török, B. *Adv. Synth. Catal.* **2005**, *347*, 1797.

16. Szöllösi, G.; Török, B.; Baranyi, L.; Bartók, M. *J. Catal.* **1998**, *179*, 619; Balázsik, K.; Török, B.; Szakonyi, G.; Bartók, M. *Appl. Catal. A* **1999**, *182*, 53; Török, B.; London, G.; Bartók, M. *Synlett* **2000**, 631.

17. Cseri, T.; Békássy, S.; Figueras, F.; Cseke, E.; de Ménorval, L.-C.; Dutatre, R. *Appl. Catal. A* **1995**, *132*, 141.

18. Cativiela, C.; Figueras, F.; Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; de Ménorval, L.-C.; Pires, E. *Appl. Catal. A* **1993**, *101*, 253; Török, B.; Szöllösi, Gy.; Rózsa-Tarjáni, M.; Bartók, M. *Mol. Cryst. Liquid Cryst.* **1998**, *311*, 289.

19. *General method for the coupling reaction of benzylamines:* The reactions have been carried out in a focused CEM Discover Benchmate microwave reactor, using the open vessel technique. The temperature has been measured and kept constant using an infrared temperature detector/controller. Benzylamine (1 mmol) was dissolved in 10 ml of methylene chloride. K-10 montmorillonite (500 mg) was added to the mixture and then stirred for 2 min. The solvent was removed and the dry mixture was transferred into a reaction tube and inserted into the cavity of the microwave reactor. All reactions have been carried out under atmospheric pressure. The progress of the reaction was monitored by GC–MS. When the reaction was completed the product was dissolved in CH_2Cl_2, was separated from catalyst by filtration and the solvent was removed. The crude product was purified by flash chromatography. Similar procedure was followed in case of amine mixtures using 1:1 molar ratio for benzylamine and anilines and 1:2 ratio for aliphatic amines.

20. Olah, G. A.; Török, B.; Shamma, T.; Török, M.; Prakash, G. K. S. *Catal. Lett.* **1996**, *42*, 5; Beregszászi, T.; Török, B.; Molnár, A.; Olah, G. A.; Prakash, G. K. S. *Catal. Lett.* **1997**, *48*, 83.

21. Landge, S. M.; Schmidt, A.; Outerbridge, V.; Török, B. *Synlett*, in press.

22. Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913; Hjemencrantz, A.; Berg, U. *J. Org. Chem.* **2002**, *67*, 3585; Guo, J.; Frost, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 528.