

A Formal Metal-Free *N*-Arylation via the Schmidt Reaction of Aromatic Aldehydes with an Azido Amine

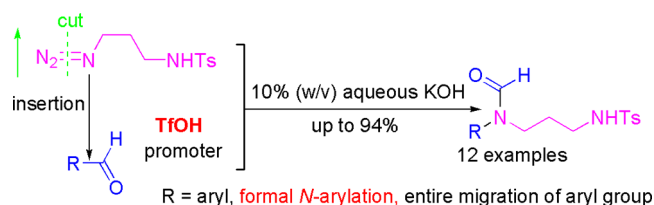
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ABSTRACT



A formal metal-free *N*-arylation of aromatic aldehydes with 3-azido-*N*-tosylpropan-1-amine through the Schmidt process was realized in the presence of acids. TfOH was found to be a good promoter, and the exclusive 1,2-aryl migration was observed. Furthermore, the conversion of an aliphatic aldehyde to the *N,N*-disubstituted formamide was achieved in excellent yield.

Aromatic amines play very important roles in the pharmaceutical, material, and dye industries,¹ which are usually made from the transition-metal-catalyzed arylation of *N*-nucleophiles with aryl halides,² arylboronic acids,³ or arenes⁴ under strong basic conditions. Due to their importance, continuous efforts have focused on the development of a new type of aromatic coupling partners. For example, the aryl carboxylic acids have been used for

copper-catalyzed decarboxylative *N*-arylation more recently.⁵ To the best of our knowledge, *N*-arylation of amines with aromatic aldehydes through a similar conversion has not been achieved. The nitrogen atom insertion into the C–C bond between the benzene ring and carbonyl group might be an alternative solution. The conversion of aldehydes to one-carbon shorter amines through the Curtius rearrangement of acyl azides has been reported,⁶ and the acyl azides were prepared in situ by oxidation of aldehydes in the presence of azide. The expected products of the aryl-migration Schmidt reaction of aryl aldehydes are aryl amines, which is a sensible option to address this issue. In this paper, we present an efficient method for the formal *N*-arylation of 3-azido-*N*-tosylpropan-1-amine with aromatic aldehydes through the Schmidt process.

(1) For recent reviews, see: (a) Fisher, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284.

(2) For selected examples, see: (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348.

(3) For selected examples, see: (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (b) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Wintres, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.

(4) For selected examples, see: (a) Tsang, W. C. P.; Zheng, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (c) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (f) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

(5) For selected examples, see: (a) Cho, C.-C.; Liu, J.-N.; Chien, C.-H.; Shie, J.-J.; Chen, Y.-C.; Fang, J.-M. *J. Org. Chem.* **2009**, *74*, 1549. (b) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (c) Ju, L.; Bode, J. W.; Toma, T.; Fukuyama, T. *Org. Synth.* **2010**, *87*, 218. (d) Zhang, Y.; Patel, S.; Mainolfi, N. *Chem. Sci.* **2012**, *3*, 3196.

(6) (a) Vora, H. U.; Moncecchi, J. R.; Epstein, O.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 9727–9731. (b) Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* **2003**, *68*, 9453–9455.

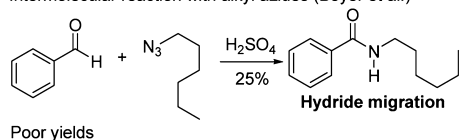
(7) For two recently reviews on the Schmidt reaction of hydrazoic acid or an alkyl azide with carbonyl compounds, see: (a) Aubé, J. In *Organic Azides: Synthesis and Applications*; Brase, S., Banert, K., Eds.; Wiley: Weinheim, 2009; pp 191–237. (b) Wroblewski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2012**, *78*, 1–320.

(8) For an intramolecular Schmidt reaction of alkyl azides with acyl chloride developed in our group, see: Gu, P.; Kang, X.-Y.; Sun, J.; Wang, B.-J.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. *Org. Lett.* **2012**, *14*, 5796–5799.

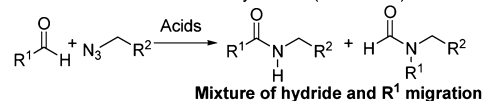
Much effort has been focused toward the Schmidt conversion of carbonyl compounds.^{7,8} The reaction of ketones with alkyl azides has been extensively explored and widely utilized in the total synthesis of natural products.^{7,9,10} In contrast, only a few examples of the Schmidt reaction of aldehydes with alkyl azides^{11–13} have been reported (Scheme 1). The reaction of aldehydes with HN₃ generally furnished a mixture of nitriles and formanilides resulting from migration of the aryl group in accepted yields.^{14,15} However when the alkyl azides were used, no formanilides from the migration of aryl groups were observed.

Scheme 1. Intermolecular Schmidt Reactions of Alkyl Azides with Aldehydes

Intermolecular reaction with alkyl azides (Boyer et al.)

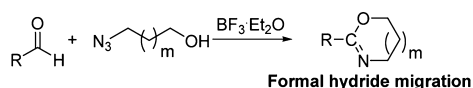


Intermolecular reaction with alkyl azides (Aubé et al.)



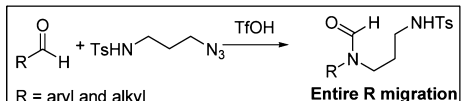
Low to moderate yields, low regioselectivities
Only aliphatic aldehydes were investigated

Modified intermolecular reaction with hydroxyl azides (Boyer et al. and Aubé et al.)



Good to excellent yields, excellent regioselectivity
Elimination of H⁺ for aromatic and aliphatic aldehydes

This work:



Theoretically, the Schmidt reaction of aromatic ketones or aromatic aldehydes with alkyl azides would give aryl

(9) For a representative intramolecular Schmidt reaction of alkyl azides with ketones, see: (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.

(10) For an intermolecular Schmidt reaction of alkyl azides with ketones, see: Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635–1637.

(11) For an intramolecular Schmidt reaction of aldehydes with alkyl azides, see: ref 9b.

(12) For the normal intermolecular Schmidt reaction of aldehydes with alkyl azides, see: Lee, H.-L.; Aubé, J. *Tetrahedron* **2007**, *63*, 9007–9015.

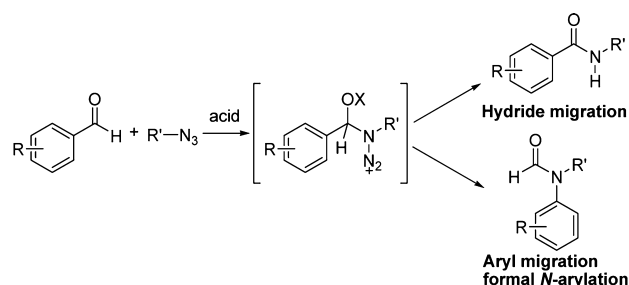
(13) For the modified intermolecular Schmidt reaction of aldehydes with azido alcohols, see: (a) Badiang, J. G.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 2484–2487. (b) Boyer, J. H.; Morgan, L. R., Jr. *J. Org. Chem.* **1959**, *24*, 561–562. (c) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325–327. (d) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951–954.

(14) For a review on a Schmidt reaction of aldehydes with HN₃, see: Koldobskii, G. I.; Ostrovskii, V. A.; Gidasov, B. V. *Russ. Chem. Rev.* **1978**, *47*, 1084–1094.

(15) For recent examples of a chemoselective Schmidt reaction of aldehydes with sodium azide to nitriles, see: Rokade, B. V.; Prabhu, K. R. *J. Org. Chem.* **2012**, *77*, 5364–5370 and references cited therein.

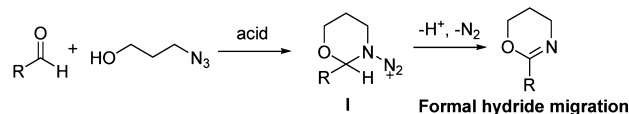
amines if the aryl migration was preferred (Scheme 2). However, the intramolecular reaction of aryl ketones was proven to be less reactive;^{9b} therefore it was easy to accept the fact that the intermolecular conversion was lacking. Previous research had revealed that aryl aldehydes were slightly more reactive than aryl ketones for the intermolecular reaction with alkyl azides, with release of benzamides by hydride migration.^{13b–d} Aubé and co-workers reported that the reaction of aliphatic aldehydes in the presence of Lewis acids gave better results, albeit in poor regioselectivities (alkyl shift vs hydride shift).¹²

Scheme 2. Promised Products from the Intermolecular Schmidt Reaction of Aryl Aldehydes with Alkyl Azides



Following their continuing projects on the modified intermolecular reaction of ketones,¹⁶ Aubé and co-workers presented the conversion of aromatic aldehydes with azido alcohols to heterocycles in good yields.¹³ The products could be thought to be derived from the formal hydride migration, although elimination of H⁺ and N₂ of the key azidohydrin intermediate (**I**) was preferred by these authors (Scheme 3).^{13a} The strong migration aptitude of the aryl group had been observed in the Schmidt reaction of carbocations with alkyl azides,¹⁷ thus it was very interesting that no amides from the competitive aryl migration were found in the reactions of aryl aldehydes with alkyl azides or azido alcohols.

Scheme 3. Regioselectivity of Schmidt Reactions of Aldehydes with 1,3-Azido Alcohol



In order to attain the *N*-arylation products, the Schmidt process should be controlled through the exclusive 1,2-aryl

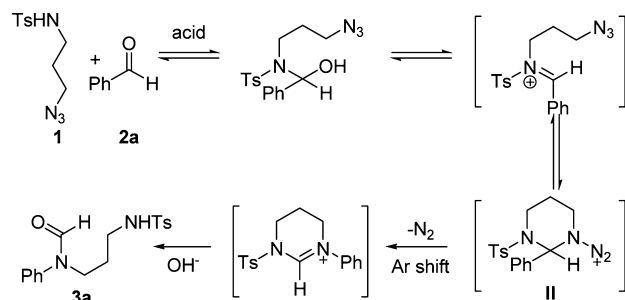
(16) (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047. (b) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 10. (c) Forsee, J. E.; Aubé, J. *J. Org. Chem.* **1999**, *64*, 4381. (d) Forsee, J. E.; Aubé, J. *Org. Lett.* **1999**, *1*, 495. (e) Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771. (f) Katz, C. E.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948. (g) Sahasrabudhe, K.; Gracias, V.; Fumess, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914.

(17) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194.

migration from the azidoalcohol intermediate. The intermolecular Schmidt reaction of aldehydes had been reported to be less effective,¹² so we paid more attention to the modified procedure with the azido alcohols.¹³ We decided to change the framework of the rearrangement intermediate to see if migration of the aryl group was possible. The oxygen atom in the ring of the azidoalcohol intermediate (**I**, Scheme 3) was envisioned to be replaced with a nitrogen unit (**II**, Scheme 4).

To test our proposal, the 3-azido-*N*-tosylpropan-1-amine **1** and benzaldehyde **2a** were selected for the initial investigation. As expected, the iminium cation would be formed by dehydration of the potential hemiaminals through a similar process of the reaction of 1,3-azido alcohol. Then the Schmidt reaction would proceed. If the migration of the aryl group was preferred, the *N*-aryl iminium would be formed, which could be hydrolyzed to formamide **3a**.

Scheme 4. Designed Aryl Migration Schmidt Reaction of Benzaldehyde with 3-Azido-*N*-tosylpropan-1-amine



To our delight, treatment of benzaldehyde **2a** and azide **1** with several acids followed by aqueous KOH afforded the *N,N*-disubstituted formamide **3a** (Table 1). Among the acids, triflic acid (TfOH) was proven to be effective. By increasing the amount of TfOH, the amide **3a** could be delivered in better yields (entries 6 and 7). It was believed that the two nitrogen atoms in the product would partly deactivate the promoter. The aqueous base workup with 10% KOH solution was slightly better than the 50% KOH solution (entry 8 vs 7), which might be due to the trace deformylation of **3a** under the excessively basic conditions.¹⁸ It should be noted that the entire 1,2-migration of the aromatic ring happened here.

After the opposite regioselectivity of the reaction to that of the previous conversion was achieved, we explored the scope of aldehydes (Table 2) with the optimal conditions established above (in bold, Table 1). A series of aryl aldehydes **2b–2l** were all successfully converted to the corresponding *N*-arylation amides. The structure of **3g** was confirmed by X-ray crystallographic analysis (Figure 1). Noteworthy features of the conversion include the following: (1) the entire migration of the aryl group over hydride is observed from

Table 1. Optimization of the Schmidt Reaction of Aldehyde **2a** with 3-Azido Amine **1**^a

entry	acid	reaction time (h)	yield ^b (%)
1	TiCl ₄ (1.1 equiv)	6	13
2	SnCl ₄ (1.1 equiv)	6	31
3	BF ₃ ·OEt ₂ (1.1 equiv)	6	14
4	TFA (1.1 equiv)	12	0
5	TfOH (1.1 equiv)	1	54
6	TfOH (1.5 equiv)	1	64
7	TfOH (2.3 equiv)	1	89
8	TfOH (2.3 equiv)	1	91^c

^a Treatment of benzaldehyde (1.0 mmol) in DCM (5 mL) with 3-azido-*N*-tosylpropan-1-amine (1.0 mmol) with acids in the table.
^b Isolated yield after the basic workup with 50% (w/v) aqueous KOH solution.
^c Isolated yield after the basic workup with 10% (w/v) aqueous KOH solution.

the reaction of aryl aldehydes; (2) all the aryl aldehydes except the 4-methoxy benzaldehyde exhibit good to excellent reactivities; and (3) the methoxyl group of 4-methoxy benzaldehyde might limit the formation of hemiaminal as well as the attack of azide to the iminium, which seriously affects the production of formamide (entry 9, Table 2).

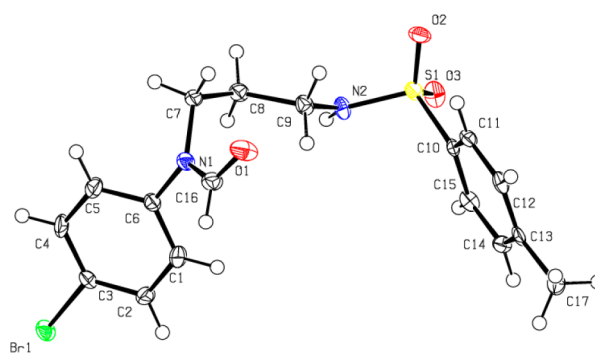


Figure 1. X-ray structure of formamide **3g**.

To extend the transformation, conversion of an aliphatic aldehyde **2m** with the azido amine was also investigated (Scheme 5), and the *N,N*-disubstituted formamide **3m** was successfully obtained in 91% yield with complete migration of the alkyl group.

Two alkyl azides, including the benzyl azide and *n*-heptyl azide, had been used to react with benzaldehyde with the promotion of TfOH as the control experiments, but both of them resulted in very complicated mixtures. From the NMR analysis of the crudes, only trace signals of the

(18) For an example of deformylation of formamide under the basic condition, see: Hengartner, U.; Batcho, A. D.; Blount, J. F.; Leimgruber, W.; Larscheid, M. E.; Scott, J. W. *J. Org. Chem.* **1979**, *44*, 3748.

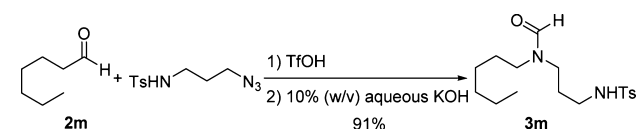
Table 2. Scope of the Conversion^a

entry	aldehydes 2	3	yield ^b (%)
1	2a , R = Ph	3a	91
2	2b , R = 4-Me-Ph	3b	71
3	2c , R = 4-Et-Ph	3c	92
4	2d , R = 4- ⁱ Pr-Ph	3d	86
5	2e , R = 4-F-Ph	3e	81
6	2f , R = 4-Cl-Ph	3f	94
7	2g , R = 4-Br-Ph	3g	85
8	2h , R = 4-CN-Ph	3h	87
9	2i , R = 4-OMe-Ph	3i	14
10	2j , R = 3-OMe-Ph	3j	94
11	2k , R = 1-Naphenyl	3k	78
12	2l , R = 2-Naphenyl	3l	91

^a Reaction of the aldehyde **2** (1.0 mmol) and 3-azido-*N*-tosylpropan-1-amine **1** (1.0 mmol) in DCM (10 mL) in the presence of TfOH (2.3 mmol, 2.3 equiv) for 60 min followed by treatment of 10% (w/v) aqueous KOH solution (5 mL) for 60 min. ^b Isolated yield.

possible amides could be found (<5%). We tried to separate them from the mixtures but failed. So the amino group of 3-azido-*N*-tosylpropan-1-amine would be essential for the aryl- and alkyl-migration Schmidt reactions of aldehydes based on consideration of the reaction yields presented above.

In conclusion, we have developed an efficient conversion of aldehydes to formamides by using 3-azido-*N*-tosylpropan-1-amine through the Schmidt process in the presence of TfOH. The migration of an aryl and alkyl group over

Scheme 5. Schmidt Reaction of the Aliphatic Aldehyde **2m** with 3-Azido-*N*-tosylpropan-1-amine

hydride was observed in the rearrangement process, with the formal *N*-arylation or *N*-alkylation of formamides being obtained in good to excellent yields in most cases. Extensive research will be undertaken to understand why the Schmidt reaction of aldehydes with the 3-azido-*N*-tosylpropan-1-amine proceeds so differently from that with azido alcohols.

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Supporting Information Available. Experimental procedures and spectroscopic data and copies of NMR spectra for all new compounds and X-ray crystallographic data for compound **3g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.