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Selective Synthesis of mono- and di-Methylated Amines using Methanol and Sodium Azide as C1 and N1 Sources

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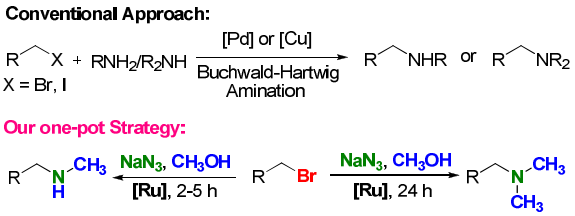
A Ru(II) complex mediated synthesis of various N,N-dimethyl and N-monomethyl amines from organic azides using methanol as a methylating agent is reported. The methodology was successfully applied for the one-pot reaction of bromide derivatives and sodium azide in methanol. Notably, by controlling the reaction time several N-monomethylated and N,N-dimethylated amines were synthesized selectively. The practical applicability of this tandem process was revealed by preparative scale reactions with different organic azides and synthesis of anti-vertigo drug betahistine. Several kinetic experiments and DFT studies were carried out to understand the mechanism of this transformation.

Introduction

Utilization of inexpensive and abundant methanol as a fuel, hydrogen storage medium and feedstock to produce various value-added chemicals such as biofuels, amino acids, and polymers became highly relevant in recent years as the crude oil reserves are depleting rapidly.[1-3] In addition to this, sustainable transformation of methanol as C1 building blocks also received significant attention in organic synthesis.[4, 5] In this prospect some remarkable advancements were achieved for the utilization of methanol in many eco-friendly reactions such as C/N-methylation,[6-12] C-methoxylation,[13] N-formylation,[14-16] and methoxycarbonylation.[17]

N-methylated amines are considered as an essential unit in numerous biologically active compounds and also serve as key intermediates in the preparation of various natural products, dyes, agrochemicals, bulk and fine chemicals.[18, 19] Traditionally for the N-methylation of amines carcinogenic methyl iodide, dimethyl sulphate, trimethyloxonium tetrafluoroborate or diazomethane, etc. were employed which generate stoichiometric amount of toxic waste.[20-22] Recently, trimethyl orthoformate, dimethyl carbonate, and dimethyl sulfoxide were also scrutinized as methylating agent but the efficiency and selectivity was poor.[23-25] Hence, for the development of sustainable methylation process utilization of methanol as a methylation agent is highly desirable.

Organic azides are highly important and versatile class of compounds in synthetic chemistry which received notable interest in last two decades due to their broad synthetic applicability as well as their easy accessibility via numerous simple and state forward protocols.[26, 27] Staudinger reaction,[28, 29] Schmidt reaction,[30, 31] Curtius rearrangement[32] and azide-alkyne Huisgen cycloaddition[33-35] are the most common classical organic reactions using azides. The reduction of azides to amines is quite well known in literature and recently few efficient methods also developed using softer reducing agents.[36-42] Multistep transformations of organic azides to N-methylated amines using toxic MeI or paraformaldehyde/$NaBH_4$ is known in literature.[43, 44] Remarkably, Hong group demonstrated Ru(II) complex catalyzed synthesis of amide from azide and alcohol which is the only example known till date for the azide alcohol coupling.[45]



Scheme 1 Methodology for synthesis of N-Methylated amines.

In our continued interest to develop atom-economical and environmentally benign protocols to construct new C-C and C-N bonds by alcohol activation, herein we report a Ru(II) complex catalyzed tandem transformation of various aromatic and aliphatic azides into the corresponding N-methylated amines. To the best of our knowledge, direct conversion of organic azides to N-methylated amines using methanol is not reported yet (Scheme **1**).

Result and Discussion

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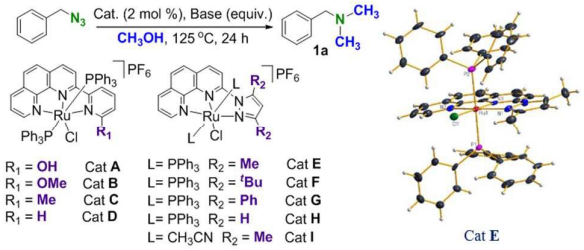
Initially, reaction of benzyl azide with methanol was tested as a model reaction in presence of various 1,10-phenanthroline based tridentate NNN pincer Ru(II) complexes (2 mol %) which showed 23-40% yields of N,N-dimethylbenzyl amine after 24 h (Table **1,** entries **1-4**). Compared to our previous studies with methanol activation,[7] among the phen-py based Ru(II) complexes (**A-D**), 2-hydroxypyridine moiety containing complex **A** did not show better activity which suggested that the metal-ligand cooperativity was not the dominating factor in this reaction. To improve the catalytic activity and make the ligand more electron rich, different substituted pyrazole[46, 47] units were introduced at the 2-position of the 1, 10-phenanthroline moiety which yielded stable NNN-pincer ligands. The corresponding Ru(II) complexes were synthesized in good yields by reacting an equimolar amount of phen-pyra ligands (**1b-1d**) with $RuCl_2(PPh_3)_3$ in refluxing methanol under inert atmosphere followed by anion metathesis with NH_4PF_6 (SI, Scheme S1 and S2). These complexes were fully characterized by different spectroscopic techniques and the solid state structure of complex **E** also confirmed the geometry around the Ru center. Afterward, these new Ru(II) complexes (**E-I)** were also screened and we were pleased to find that complex **E** delivered the highest yield of N,N-dimethylbenzyl amine among all the Ru(II) complexes (Table **1,** entry **5**). Different weak and strong bases were screened with complex **E** and NaOH (1.5 equiv.) gave the best yield (67%) of N,N-dimethylbenzyl amine at 125 °C within 24 h (SI, Table S2). Common Ru(II) precursors like $Ru(H_2)(CO)(PPh_3)_3$, $Ru(H)(Cl)(CO)(PPh_3)_3$, $RuCl_2(PPh_3)_3$ were also tested, which displayed lower activity compared to the complex **E** (SI, Table S1). There was no product formation in the absence of any Ru(II) complex. When the catalyst loading was increased up to 3 mol %, to our delight complex **E** delivered the desired amine **1a** in 98% yield (Table **1**, entry **12**).

Table 1 Transformation of benzyl azide to N,N-dimethyl-1-phenylmethanamine[a]

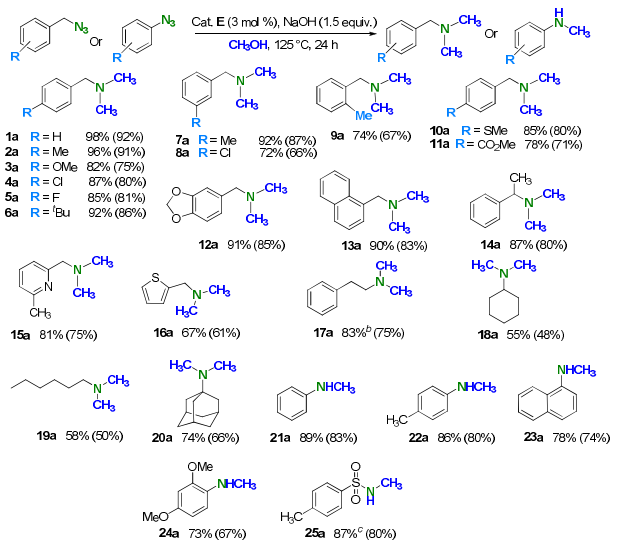


Entry	Catalyst	Base (equiv.)	Yield of **1a** (%)
1	A	KO^{t}Bu (1.0)	26
2	B	KO^{t}Bu (1.0)	37
3	C	KO^{t}Bu (1.0)	40
4	D	KO^{t}Bu (1.0)	23
5	E	KO^{t}Bu (1.0)	50
6	F	KO^{t}Bu (1.0)	42
7	G	KO^{t}Bu (1.0)	32
8	H	KO^{t}Bu (1.0)	28
9	I	KO^{t}Bu (1.0)	29
10	E	NaOH (1.0)	61
11	E	NaOH (1.5)	67
12[b]	E	NaOH (1.5)	98

[a]Reaction conditions: azide (0.375 mmol), Cat. (2 mol %), base (equiv.), methanol (1.5 mL), 24 h, 125 °C (oil bath temperature). GC yields. [b]3 mol % Cat. **E** was used.

After optimizing the reaction conditions with benzyl azide this methodology was extended to different benzyl, aryl, aliphatic and carbonyl azide substrates. Different benzyl azide substrates with electron donating and withdrawing groups at the *para, meta* and *ortho* positions were effectively converted to the corresponding substituted N,N-dimethyl-1-phenylmethanamine derivatives (Table **2**, entries **1a**-**9a**). Naphthalene, 1,3-dioxolyl, and ester substituted azides were effectively converted to the preferred products (Table **2**, entries **10a**-**12a**). Challenging heteroatomic, aliphatic, tertiary and secondary azides also responded well in this reaction conditions and produced the respective N,N-dimethyl amines in moderate to good yields (Table **2**, entries **13a**-**20a)**. Additionally, different aromatic and sulfonyl azides were also smoothly converted to the N-monomethylated products following this protocol (Table **2**, entries **21a**-**25a)**.

Table 2 Synthesis of N,N-dimethylated amines from azides[a]



[a]Reaction conditions: Azides (1.13 mmol), Cat. **E** (3 mol %), NaOH (1.69 mmol), methanol (4.5 mL), 24 h, 125 °C (oil bath temperature). [b]4 mol % Cat. **E** was used and heated for 36 h. [c]KO^{t}Bu (1.5 equiv.) was used as base. GC yields (isolated yields in parenthesis).

Notably, following the same protocol with benzyl azide at shorter reaction time (2h) formation N-methyl-1-phenylmethanamine was detected as a major product. Next, utilizing this methodology complex **E** catalyzed selective synthesis of N-monomethylated amines from organic azides was investigated by controlling the reaction time (Table **3**). Both electron donating and withdrawing group containing

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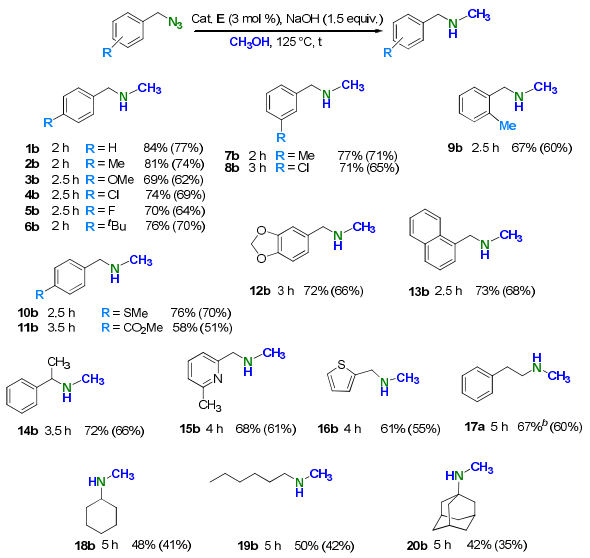
azide substrates responded well in this condition (Table **3**, entries **2b-10b**). Additionally, naphthalene, 1,3-dioxolyl and ester substituted azides were selectively converted to the desired monomethylated products in good yields (Table **3**, entries **11b**-**13b**). Secondary and heteroatomic azide derivatives delivered good yields of the corresponding products under this reaction condition (Table **3**, entries **14b**-**16b**). Whereas with aliphatic and tertiary azides yields of the respective N-monomethylated amines were moderate (Table **3**, entries **17b**-**20b**).

Table 3 Scope of N-monomethylation[a]

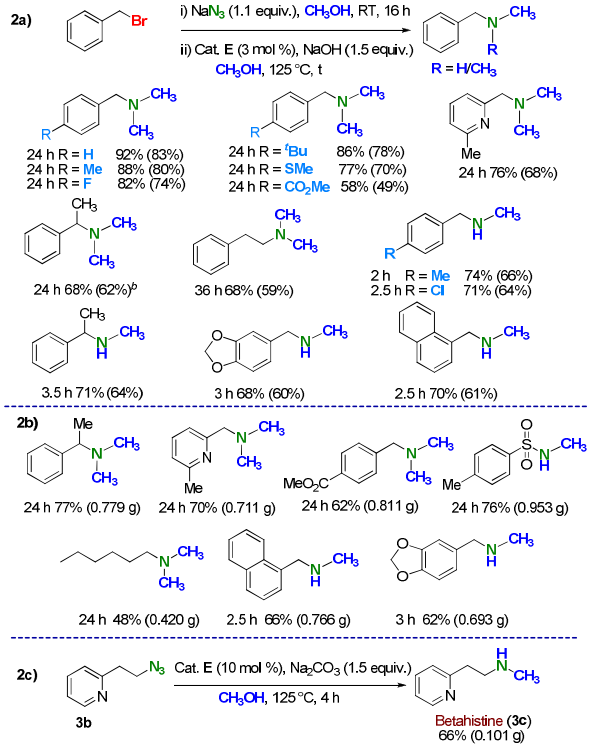


[a]Reaction conditions: Azides (1.13 mmol), Cat. **E** (3 mol %), NaOH (1.69 mmol), methanol (4.5 mL), time, 125 °C (oil bath temperature). GC yields (isolated yields in parenthesis). [b]4 mol % Cat. **E** was used.

To reveal the practical applicability of this methodology one-pot N,N-dimethylation and N-monomethylation of several benzyl and aliphatic bromides using sodium azide and methanol were investigated. For this purpose, benzyl bromide was taken as a model substrate and the reaction was carried out in the presence of NaN_3 (1.1 equiv.) in methanol at room temperature for 16 h followed by addition of Ru(II) catalyst (**E**) and NaOH which furnished the N,N-dimethyl-1-phenylmethanamine in excellent yields (SI, Table S8). Afterward, this one-pot protocol was successfully applied to a wide range of benzyl bromide derivatives, heteoatomic substrates as well as aliphatic substrates which delivered the desired products in good to excellent yields (Scheme **2a**).

Next, we extended this sustainable protocol to preparative scale synthesis of methylated amines. Aromatic, aliphatic and heteroatomic azide substrates were successfully converted to the respective mono and dimethylated amine derivatives in good to moderate yields (Scheme **2b**). Moreover, this methodology was employed in the N-monomethylation of 2-(2-azidoethyl)pyridine to synthesize N-methyl-2-(pyridin-2-yl)ethanamine (betahistine) which is used as a drug for the treatments of Meniere's disease and vertigo symptoms (Scheme **2c**, entry **3c**).[48, 49]

To shed some light on the mechanism of this reaction, time dependent product distribution during the tandem transformation of azides to N-methylated amines was monitored (Figure **1**). Within 30 minutes, benzyl azide was



Scheme 2 Practical applicability of the methodology: **2a**) One-Pot methylation of bromide derivatives; **2b**) Preparative scale synthesis of N-methylated amines; **2c**) Synthesis of betahistine.

consumed and benzyl amine appeared as a major product along with a small amount of N-methyl-1-phenylmethanamine (Figure **1a**). Then, gradually benzyl amine was converted to N-methyl-1-phenylmethanamine and within 2 h its concentration reached the maxima (~84%). N,N-dimethyl-1-phenylmethanamine concentration was considerably low within first 2 h which slowly increased during the course of the reaction and reached maxima after 24 h (Figure **1b**). This clearly implies that rate of the N-monomethylation reaction was much faster than the N,N-dimethylation reaction.

The formation of phenylmethanimine intermediate during the conversion of benzyl azide to benzyl amine is well documented in literature.[50, 51] To detect the phenylmethanimine intermediate in our reaction condition we monitored the conversion of benzyl azide in presence of Cat. **E** in 2-propanol up to seven days at room temperature and as well as after heating at 85 °C for 12 h. However, under both conditions we did not detect any phenylmethanimine. Hence, we synthesized the active Ru-H complex (Cat. **EH**) by treating the precatalyst **E** with NaO^iPr in 2-propanol/dichloromethane mixture (2:1) at 82 °C (SI, page 22). This Ru-H species (Cat. **EH**)

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was characterized by ^{31}P and ^{1}H NMR spectroscopy (SI, Figure S3 and S4). The ^{31}P NMR resonance of the complex **EH** was observed at δ = 50.18 ppm and in ^{1}H NMR spectroscopy it gave a hydride resonance at δ = -5.88 ppm (t, $J_{H\text{-}P}$ = 24.6 Hz). Afterward, the same experiment for the detection of phenylmethanimine intermediate was repeated with this Ru-H species (Cat. **EH**) at room temperature and the reaction was monitored up to seven days (SI, Figure S5). After three days at room temperature stirring 15% conversion of benzyl azide to phenylmethanimine (7%) and N-benzylidene-1-phenylmethanamine (8 %) was detected (SI, Figure S5). Due to high reactivity of the phenylmethanimine it was readily coupled with in-situ generated benzyl amine and formed N-benzylidene-1-phenylmethanamine (SI, Scheme S9).[51] For that reason although the conversion of benzyl azide after seven days was 30% the effective concentration phenylmethanimine was never increased beyond 11% (SI, Scheme S9 and Figure S5). Similar phenomenon was also observed when this reaction was carried out at 85 °C in 2-propanol (SI, Scheme S9 and Figure S6). This experiment clearly suggested the involvement of the Ru-H species (Cat. **EH**) in the conversion of benzyl azide to phenylmethanimine which is the intermediate for the formation of benzyl amine.[50-52]

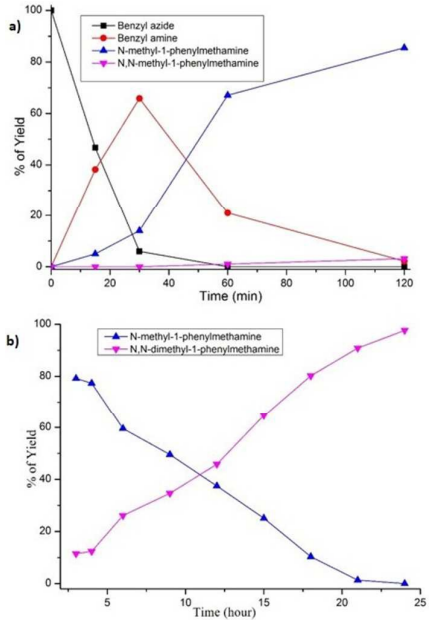
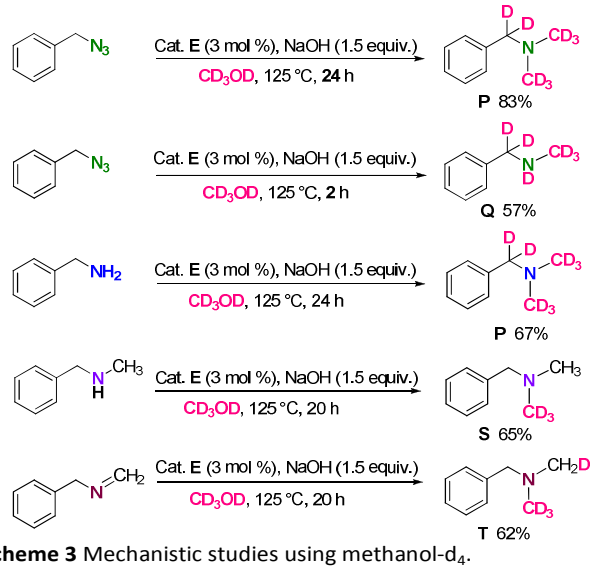


Figure 1. Time dependent product distribution studies of benzyl azide: **a)** 0-120 minutes, **b)** 2-24 hours.

Next, several kinetic experiments with benzyl azide and various intermediates using methanol-d_4 were performed (Scheme **3**). With benzyl azide and benzyl amine deuterated N,N-dimethylbenzyl amine (**P**) was formed as the major product in methanol-d_4. Notably, for both of these reactions α-CH_2 of the final product was fully deuterated. This exchange transpired probably through phenylmethanimine intermediate followed by Ru(II) complex catalyzed 1,3-deuteride transfer process (SI, Scheme S11). For the Ru(II) complex catalyzed α-deuteration of amines, Szymczak and Gunanathan groups also proposed similar 1,3-deuteride migration to imine.[53-56] We hypothesized that in presence of complex **E** benzyl azide would smoothly convert to phenylmethanimine which is well documented in the literature.[51, 52, 57] In addition, the reaction of N-methylbenzyl amine and N-methylene-1-phenylmethanamine in methanol-d_4 yielded partially deuterated products **S** and **T**. On the basis of these kinetic and deuterium experiments a probable catalytic cycle was proposed for this system (SI, Scheme S10).



Scheme 3 Mechanistic studies using methanol-d_4.

For better understanding the reaction mechanism a detail DFT calculations for the conversion of benzyl azide to N-methylated amine in methanol was carried out (Figure **2**). The reaction mechanism can be divided into four parts: (a) methanol dehydrogenation, (b) generation of imine form azide (via 1,2-proton shift), (c) imine hydrogenation and (d) N-methylene imine hydrogenation (Figure **2**). Firstly, the methoxy complex (**I1**) was generated from the starting complex **E** via base mediated activation (Figure **2**). Then, one of the PPh_3 dissociated from the intermediate **I1** which destabilized the system (**I2**) by 12.29 kcal/mol. Afterward, β-H elimination (**TS1**) from the intermediate **I2** furnished a metal-hydride complex (**I3**) with the activation energy barrier of 7.7 kcal/mol which subsequently converted to the azide bound intermediate **I4** (17.50 [37.90] kcal/mol) via the substitution of formaldehyde molecule. Then, N_2 elimination followed by 1,2-proton shift provided the intermediate **I5** where the imine was bound to metal center in η^2-fashion. Afterward, the insertion of the imine molecule into the metal-hydride bond through the four membered transition state (**TS2** with activation energy barrier of 3.68 kcal/mol) followed by methanolysis furnished the amine. The resulting amine was coupled with formaldehyde (produced from dehydrogenation of methanol) and yielded N-methylene-1-phenylmethanamine (SI, Scheme S10). Then, this N-methylene-1-phenylmethanamine was hydrogenated by the Ru-H with activation barrier of 3.60 kcal/mol (**TS3**) and produced the desired N-methylbenzyl amine product (Figure **2**). This N-monomethylated amine can

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be converted to the N,N-dimethylbenzylamine following another catalytic cycle. In this catalytic cycle methanol dehydrogenation process required comparably higher activation energy (7.7 kcal/mol) than the imine and N-methylene imine hydrogenation steps.

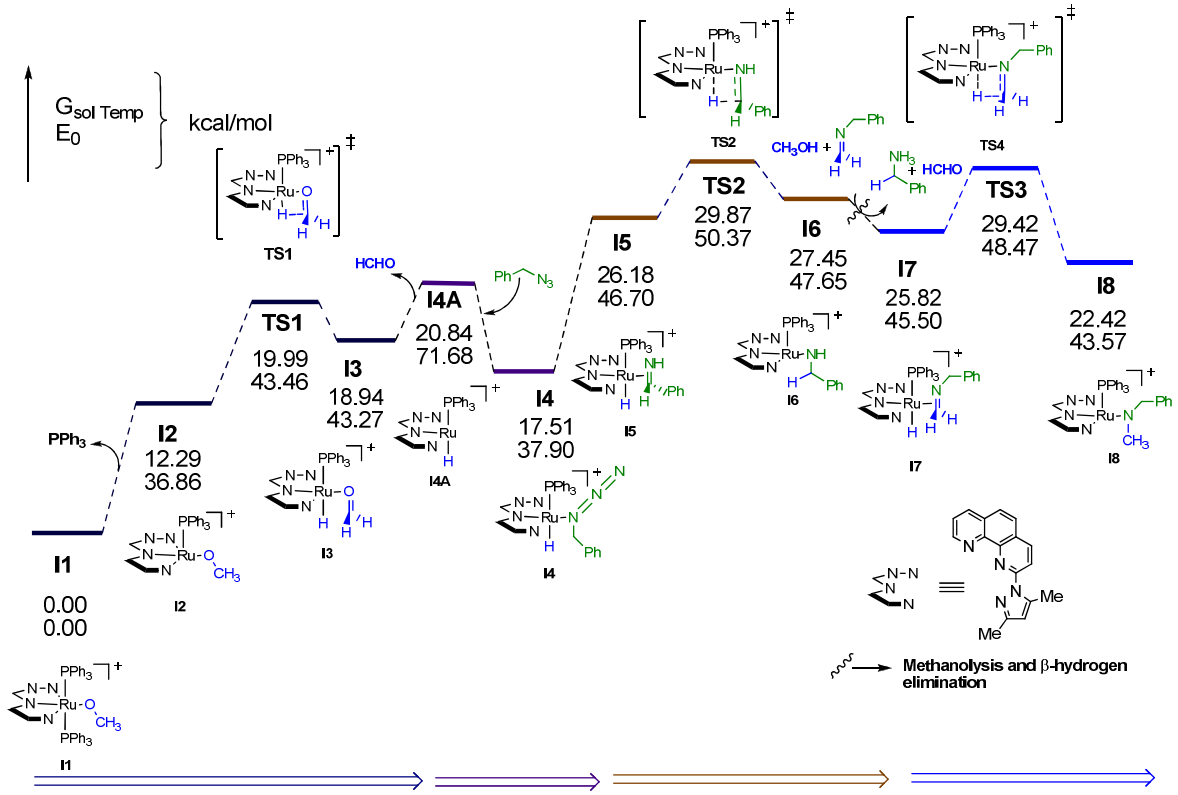

Figure 2. Calculated Gibbs free energies and enthalpies (kcal/mol) for the formation of N-methylated amines from benzyl azide using methanol (Hybrid functional, M06-2X was used with the LANL2DZ basis set for Ru and 6-31G** basis set for nonmetal elements). Steps involve for the conversion of **I6** to **I7** are shown in SI Figure **S7**.

Conclusions

In summary, we developed a Ru(II) complex catalyzed tandem as well as sustainable process for the synthesis of various N,N-dimethylated and N-monomethylated amines from organic azides. To best of our knowledge, this is the first example where combination of organic azides and methanol were utilized as N1 and C1 sources respectively for the synthesis of N-methylated amine products. Notably, following this methodology varieties of N-methylamine and N,N-dimethylamine were selectively synthesized in one-pot fashion using bromide derivatives and inexpensive sodium azide in methanol. The practical applicability of this protocol was also explored by synthesizing methylated amines in large scale quantity. Additionally, this methodology was successfully employed for the synthesis anti-vertigo drug betahistine. Several kinetic experiments and DFT studies were carried out to understand the mechanistic aspect of this tandem transformation. An air and moisture-stable ruthenium complex catalyzed this alternative approach provides a practical and efficient method for the selective synthesis of N-methylated amines from azides and methanol.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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1. G. A. Olah, A. Goeppert and G. K. S. Prakash, *Beyond Oil and Gas: The Methanol Economy, Second Edition*, WILEY-VCH, Weinheim, 2009.
2. G. A. Olah, *Angew. Chem. Int. Ed.*, 2005, **44**, 2636-2639.
3. G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611-1641.
4. K. Natte, H. Neumann, M. Beller and R. V. Jagadeesh, *Angew. Chem. Int. Ed.*, 2017, **56**, 6384-6394.
5. R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437-1451.
6. Z. Liu, Z. Yang, X. Yu, H. Zhang, B. Yu, Y. Zhao and Z. Liu, *Org. Lett.*, 2017, **19**, 5228-5231.
7. K. Chakrabarti, M. Maji, D. Panja, B. Paul, S. Shee, G. K. Das and S. Kundu, *Org. Lett.*, 2017, **19**, 4750-4753.
8. T. T. Dang, B. Ramalingam and A. M. Seayad, *ACS Catal.*, 2015, **5**, 4082-4088.
9. B. Paul, S. Shee, K. Chakrabarti and S. Kundu, *ChemSusChem*, 2017, **10**, 2370-2374.
10. T. Oku, Y. Arita, H. Tsuneki and T. Ikariya, *J. Am. Chem. Soc.*, 2004, **126**, 7368-7377.
11. L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy and T. J. Donohoe, *Angew. Chem. Int. Ed.*, 2014, **53**, 761-765.
12. S. Elangovan, J. Neumann, J.-B. Sortais, K. Junge, C. Darcel and M. Beller, *Nat. Commun.*, 2016, **7**, 12641.
13. S. Gowrisankar, H. Neumann and M. Beller, *Chem. Eur. J.*, 2012, **18**, 2498-2502.
14. N. Ortega, C. Richter and F. Glorius, *Org. Lett.*, 2013, **15**, 1776-1779.
15. S. Tanaka, T. Minato, E. Ito, M. Hara, Y. Kim, Y. Yamamoto and N. Asao, *Chem. Eur. J.*, 2013, **19**, 11832-11836.
16. B. Kang and S. H. Hong, *Adv. Synth. Catal.*, 2015, **357**, 834-840.
17. Q. Liu, K. Yuan, P.-B. Arockiam, R. Franke, H. Doucet, R. Jackstell and M. Beller, *Angew. Chem. Int. Ed.*, 2015, **54**, 4493-4497.
18. H. C. Hailes, *Appl. Organomet. Chem.*, 2001, **15**, 315-315.
19. A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, Weinheim, 5th edn., 2008.
20. M. B. Smith and J. March, *Advanced Organic Chemistry, 6th ed.*, Wiley-Interscience, New Jersey, 2007.
21. M. Selva and A. Perosa, *Green Chem.*, 2008, **10**, 457-464.
22. H. Wang, S. Yu, Z. Qi and X. Li, *Org. Lett.*, 2015, **17**, 2812-2815.
23. P. Tundo and M. Selva, *Acc. Chem. Res.*, 2002, **35**, 706-716.
24. J. R. Cabrero-Antonino, R. Adam, K. Junge and M. Beller, *Catal. Sci. Technol.*, 2016, **6**, 7956-7966.
25. X. Jiang, C. Wang, Y. Wei, D. Xue, Z. Liu and J. Xiao, *Chem. Eur. J.*, 2014, **20**, 58-63.
26. *The chemistry of the azido group (Ed.: S. Patai)* Wiley, New York, 1971.
27. S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem. Int. Ed.*, 2005, **44**, 5188-5240.
28. J. E. Leffler and R. D. Temple, *J. Am. Chem. Soc.*, 1967, **89**, 5235-5246.
29. S. Liu and K. J. Edgar, *Biomacromolecules*, 2015, **16**, 2556-2571.
30. J. Aube and G. L. Milligan, *J. Am. Chem. Soc.*, 1991, **113**, 8965-8966.
31. G. I. Koldobskii, V. A. Ostrovskii and B. Z. Gidaspov, *J. Heterocycl. Chem.*, 1975, **11**, 626-635.
32. E. C. Franklin, *Chem. Rev.*, 1934, **14**, 219-250.
33. M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952-3015.
34. C. Le Droumaguet, C. Wang and Q. Wang, *Chem. Soc. Rev.*, 2010, **39**, 1233-1239.
35. C. O. Kappe and E. Van der Eycken, *Chem. Soc. Rev.*, 2010, **39**, 1280-1290.
36. *Comprehensive Organic Functional Group Transformations*, Pergamon Press (Elsevier Science Ltd.), New York, 1995.
37. V. Udumula, S. H. Nazari, S. R. Burt, M. N. Alfindee and D. J. Michaelis, *ACS Catal.*, 2016, **6**, 4423-4427.
38. D. Cantillo, M. M. Moghaddam and C. O. Kappe, *J. Org. Chem.*, 2013, **78**, 4530-4542.
39. N. Arai, N. Onodera and T. Ohkuma, *Tetrahedron Lett.*, 2016, **57**, 4183-4186.
40. H. Saneyoshi, T. Ochikubo, T. Mashimo, K. Hatano, Y. Ito and H. Abe, *Org. Lett.*, 2014, **16**, 30-33.
41. I. Bosch, A. M. Costa, M. Martín, F. Urpí and J. Vilarrasa, *Org. Lett.*, 2000, **2**, 397-399.
42. N. Chandna, F. Kaur, S. Kumar and N. Jain, *Green Chem.*, 2017, **19**, 4268-4271.
43. H. Kato, K. Ohmori and K. Suzuki, *Synlett*, 2001, **2001**, 1003-1005.
44. S. Ayesa, B. Samuelsson and B. Classon, *Synlett*, 2008, **2008**, 97-99.
45. Z. Fu, J. Lee, B. Kang and S. H. Hong, *Org. Lett.*, 2012, **14**, 6028-6031.
46. A. Satake and T. Nakata, *J. Am. Chem. Soc.*, 1998, **120**, 10391-10396.
47. S. O. Ojwach, I. A. Guzei, L. L. Benade, S. F. Mapolie and J. Darkwa, *Organometallics*, 2009, **28**, 2127-2133.
48. M. Lacour, P. H. van de Heyning, M. Novotny and B. Tighilet, *Neuropsychiatr. Dis. Treat.*, 2007, **3**, 429-440.
49. X. Cui, X. Dai, Y. Deng and F. Shi, *Chem. Eur. J.*, 2013, **19**, 3665-3675.
50. Y. Kim, Y. H. Rhee and J. Park, *Org. Biomol. Chem.*, 2017, **15**, 1636-1641.
51. J. H. Lee, S. Gupta, W. Jeong, Y. H. Rhee and J. Park, *Angew. Chem. Int. Ed.*, 2012, **51**, 10851-10855.
52. L. Hu, Y. A. Liu and X. Liao, *Sci. Adv.*, 2017, **3**, e1700826.
53. B. Chatterjee, V. Krishnakumar and C. Gunanathan, *Org. Lett.*, 2016, **18**, 5892-5895.
54. L. V. A. Hale and N. K. Szymczak, *J. Am. Chem. Soc.*, 2016, **138**, 13489-13492.
55. T. Masaaki, O. Koichiro and M. Seijiro, *Chem. Lett.*, 2005, **34**, 192-193.
56. E. Alexakis, M. J. Hickey, J. R. Jones, L. P. Kingston, W. J. S. Lockley, A. N. Mather, T. Smith and D. J. Wilkinson, *Tetrahedron Lett.*, 2005, **46**, 4291-4293.
57. W. Jeong, J. H. Lee, J. Kim, W. J. Lee, J.-H. Seong, J. Park and Y. H. Rhee, *RSC Adv.*, 2014, **4**, 20632-20635.

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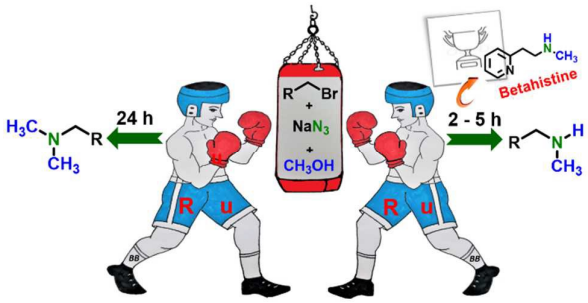
TOC



Selective synthesis of various N,N-dimethylated and N-monomethylated amines from organic azides using methanol as a methylating agent is reported.