Diazo Compounds

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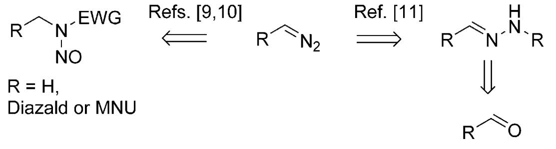
Batch and Continuous-Flow One-Pot Processes using Amine Diazotization to Produce Silylated Diazo Reagents

*Clément Audubert, Oscar Javier Gamboa Marin, and Hélène Lebel**

Abstract: *A novel synthesis of trimethylsilyldiazomethane ($TMSCHN_2$) by diazotization of trimethylsilylmethylamine ($TMSCH_2NH_2$) is reported using batch and continuous flow synthesis. The latter affords a daily production of 275 g (2.4 mol) of $TMSCHN_2$. Other silylated methylamines were also successfully reacted under the developed reaction conditions to furnish various silicon-bearing diazomethane reagents. The applicability of the process is highlighted by disclosure of batch and continuous flow one-pot esterification and 1,3-dipolar cycloaddition processes. Furthermore, the high-yielding esterification of carboxylic acids with silylated and substituted methylamines in continuous flow is disclosed. Finally, work-up and purification procedures are reported for the preparation of a 2-MeTHF solution of $TMSCHN_2$, which can be used in rhodium-catalyzed methylenation and homologation reactions.*

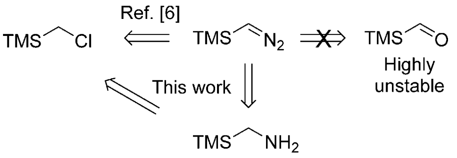
Diazo compounds are useful reagents which display a unique reactivity. Because of the release of N_2, the various addition and cycloaddition applications for which they are utilized, furnish the corresponding products in a thermodynamically irreversible fashion. However, the use of these highly reactive intermediates is often limited by safety concerns, particularly in the case of diazomethane. To overcome these issues, safer alternative reagents have been studied. For example, trimethylsilyldiazomethane ($TMSCHN_2$), an easily handled stable liquid (b.p. 96 °C), has been recognized as a safe substitute for hazardous diazomethane (CH_2N_2).[1,2] $TMSCHN_2$ has been used extensively in various reactions.[2,3] Improved chemoselectivity relative to CH_2N_2 is often observed because of the reactivity profile of the more hindered and less basic $TMSCHN_2$. For example, in the methylenation of aldehydes and ketones disclosed by our group, CH_2N_2 proved to be unreactive, whereas high yields were obtained with $TMSCHN_2$.[4,5]

The synthesis of $TMSCHN_2$ by the diazo-transfer reaction of $TMSCH_2MgCl$ with diphenyl phosphoryl azide has been largely adopted because of the facile scalability of the process.[6] Despite these advantages, a few drawbacks remain, including long reaction times (>20 h), as well as the tedious distillation of ether from $TMSCHN_2$. Continuous-flow processes[7] have been developed to safely prepare diazo reagents and mitigate some of these challenges.[8] For example, diazomethane has been generated in flow from commercially available Diazald®[9] and *N*-methyl-*N*-nitrosourea (MNU; Scheme 1).[10] The continuous flow synthesis of diazoesters and aryldiazomethanes from hydrazones has also been described.[11]



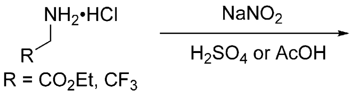
Scheme 1. Continuous-flow approaches to synthesizing diazo reagents.[9–11] EWG = electron-withdrawing group.

However, to the best of our knowledge, neither an alternative synthesis to Shioiri's procedure for $TMSCHN_2$ has been reported, nor a procedure to synthesize $TMSCHN_2$ by continuous flow (Scheme 2).[12] This deficit may be because the TMS analogue of both Diazald® and MNU is not readily available. Furthermore, the instability associated with formylsilanes[13] has precluded the use of methods involving hydrazones to prepare $TMSCHN_2$.



Scheme 2. Possible strategies to synthesize $TMSCHN_2$.

The diazotization of amines is an alternative strategy to synthesize diazo reagents and is known to be efficient for the production of electron-deficient diazo esters[14] and fluoroalkyl-substituted diazomethane[15] [Eq. (1)].[16]



(1)

Such a method has, however, not been reported in the preparation of nucleophilic diazo reagents, such as $TMSCHN_2$.[17] Herein we disclose a novel batch and continuous-flow synthesis of $TMSCHN_2$ from $TMSCH_2NH_2$. One-pot processes to perform esterification and 1,3-dipolar cycloaddition processes are described. Notably, the esterification process is compatible with other amines, including secondary

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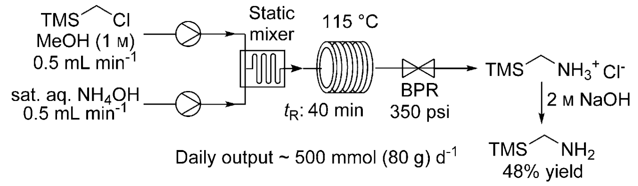
amines. Rhodium-catalyzed methylenation and homologation reactions with a process-friendly 2-MeTHF solution of $TMSCHN_2$ are also delineated.

The synthesis of $TMSCH_2NH_2$ (also commercially available) has been previously described to proceed in two steps from $TMSCH_2Cl$ via the corresponding azide reagent ($TMSCH_2N_3$).[18] An alternative and direct route would be highly desirable to avoid the use of the potentially explosive azide ($TMSCH_2N_3$), which necessitates distillation. To prepare $TMSCH_2NH_2$ in an inexpensive fashion, the reaction of $TMSCH_2Cl$ with NH_4OH in continuous flow was investigated and the targeted amine was obtained in 48 % yield following purification (Scheme 3).

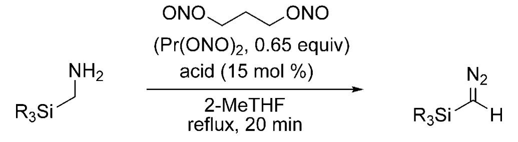


Scheme 3. Continuous-flow synthesis of $TMSCH_2NH_2$.

To mitigate this undesired byproduct, we applied a dinitrite reagent, propyldinitrite [$Pr(ONO)_2$], in 2-MeTHF to afford $TMSCHN_2$ in 62 % yield using AcOH (Table 1, entry 1).[19] Under these reaction conditions, the formation of AcOMe, although observed at the end of the reaction, was sufficiently slow to allow the production of $TMSCHN_2$. The use of the more sterically hindered 1-adamantanecarboxylic acid ($AdCO_2H$) and 4-nitrophenol ($4\text{-}NO_2C_6H_4OH$) produced $TMSCHN_2$ in 71 and 72 % yield, respectively, with a reaction time of 20 minutes (entries 2 and 3). The reaction conditions were compatible with other silylated methylamines: dimethylphenyl- and diphenylmethylsilyl diazomethane were produced under similar reactions in up to 77 and 73 % yield, respectively (entries 5 and 6).

Having established reaction conditions to synthesize $TMSCHN_2$, one-pot processes, in which the substrate is directly added to the crude solution of the diazo reagent, were studied. Such processes are highly advantageous as the starting material is a simple amine and the isolation of the diazo is avoided. For instance, esterification of various carboxylic acids proceeded in high yields (Table 2). As the reaction conditions are mild, no racemization was observed for the synthesis of esters **3**–**5** and **7**. Moreover, unprotected indoles and free alcohols were tolerated, thus furnishing esters **6** and **7** in quantitative yields.

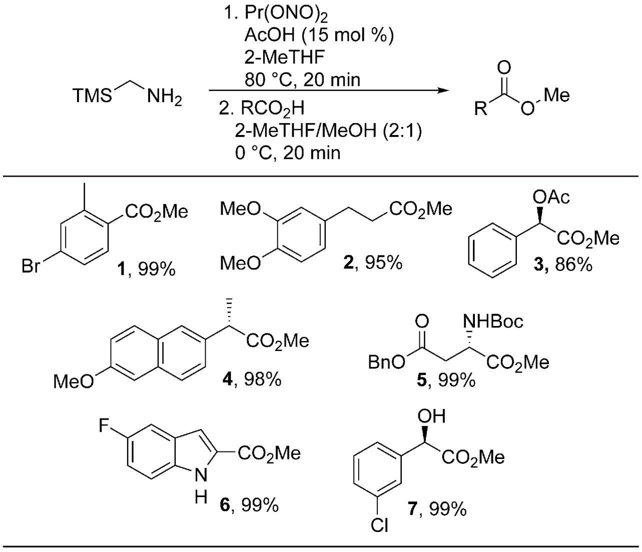
Table 1: Diazotization of $R_3SiCH_2NH_2$.



Entry	R_3Si	Acid	Yield [%][a]
1	Me_3Si	AcOH	62
2	Me_3Si	$AdCO_2H$	71
3	Me_3Si	$4\text{-}NO_2C_6H_4OH$	72
4	Me_2PhSi	$AdCO_2H$	63
5	Me_2PhSi	$4\text{-}NO_2C_6H_4OH$	77
6	$MePh_2Si$	$AdCO_2H$	73[b]
7	$MePh_2Si$	$4\text{-}NO_2C_6H_4OH$	71[c]

[a] Yield determined by ^1H NMR analysis using 1,2-diphenylethane as an internal standard. [b] Reaction time = 10 min. [c] Reaction time = 40 min. THF = tetrahydrofuran.

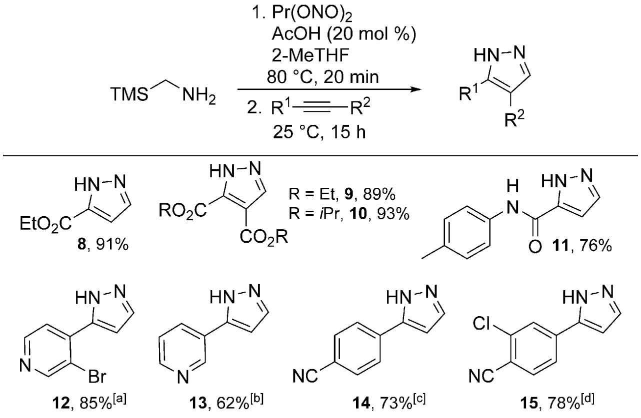
Table 2: One-pot esterification of carboxylic acids with $TMSCH_2NH_2$.



Yield is that of the isolated product. Boc = *tert*-butoxycarbonyl.

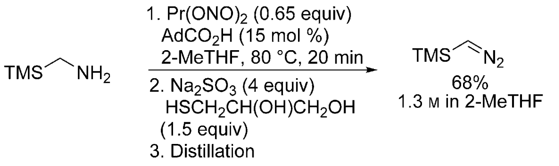
Similarly, alkynes could be added to the crude $TMSCHN_2$ mixture, and pyrazoles were produced in good to excellent yields (Table 3). Ester pyrazoles **8**–**10** were synthesized in high yields, whereas amide pyrazole **11** was obtained in good yields. Pyridine-substituted alkynes were successfully reacted to produce pyrazoles **12** and **13**. Aromatic pyrazoles **14** and **15** were also synthesized in good yields using this process.

Table 3: One-pot 1,3-dipolar cycloaddition of alkynes with $TMSCH_2NH_2$.



[a] RT, 60 h. [b] The 1,3-dipolar cycloaddition was performed in continuous flow at 100 °C for 30 min with a flow rate of 1.33 mL min^{-1}. [c] 50 °C, 36 h. [d] The 1,3-dipolar cycloaddition was performed in continuous flow at 100 °C for 15 min, then 120 °C for 15 min with a flow rate of 1.33 mL min^{-1}.

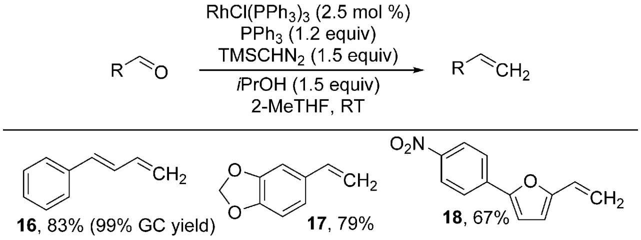
The crude reaction mixture of $TMSCHN_2$, containing nitrite residues from the diazotization, cannot always be used, as these inhibit some reactions, namely the metal-catalyzed methylenation process. A work-up procedure using a mixture of sodium sulfite and thioglycerol was thus developed to remove the nitrite residues from the $TMSCHN_2$ solution [Eq. (2)]. Distillation then afforded a 1.3 M 2-MeTHF solution of $TMSCHN_2$ with greater than 99 % purity.[19]



(2)

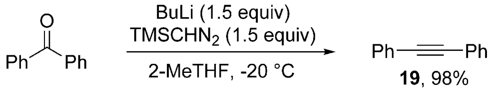
The 2-MeTHF solution of $TMSCHN_2$ was used in the rhodium-catalyzed methylenation reaction of aldehydes. The reaction conditions were compatible with 2-MeTHF (previously THF was the solvent of the reaction) and the corresponding terminal alkenes were isolated in good to excellent yields (Table 4).

Table 4: Rhodium-catalyzed methylenation of aldehydes with $TMSCHN_2$ in 2-MeTHF.



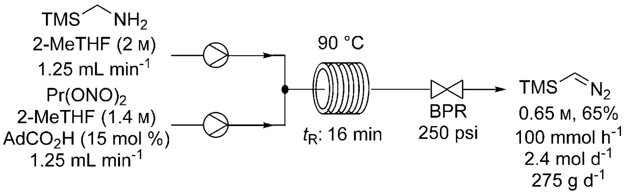
Yield is that of the isolated product.

Furthermore, the homologation of a ketone was successfully performed, thus affording the corresponding alkyne **19** in high yields [Eq. (3)].



(3)

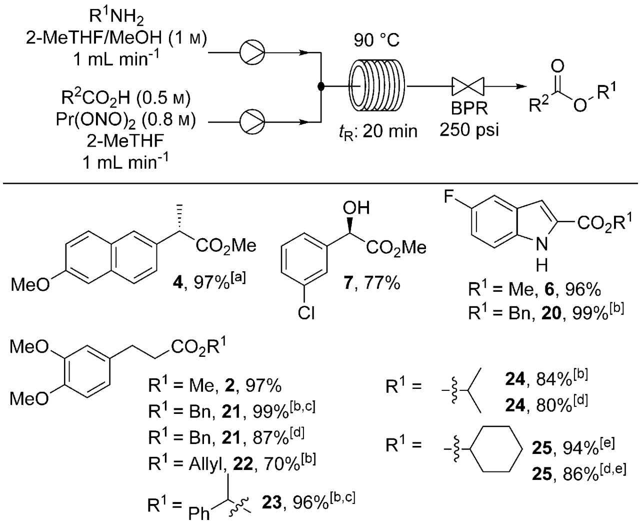
The diazotization reaction of $TMSCH_2NH_2$ was then performed in continuous flow (Scheme 4). A 0.65 M solution of $TMSCHN_2$ was produced after a 16 minute residence time, thus allowing a daily production of 2.4 mol (275 g).



Scheme 4. Continuous-flow synthesis of $TMSCH_2N_2$.

A one-pot continuous-flow esterification process[20,21] in which the carboxylic acid substrate was also used as the reagent to perform the diazotization reaction, was next developed. A solution of $TMSCH_2NH_2$ in a mixture 2-MeTHF and MeOH was mixed with a solution a propyldinitrite and the carboxylic acid substrate in 2-MeTHF, then heated at 90 °C in the reactor (Table 5). $TMSCHN_2$ was thus formed in situ and immediately consumed by the substrate in the same reactor, thus producing esters **2**, **4**, **6**, and **7** in high yields after a 20 minute residence time.[22] The versatility of this process was illustrated by the use of various substituted amines to afford benzyl esters **20** and **21**, allyl ester **22**, sterically hindered 1-phenylethyl ester **23**, isopropyl ester **24**, and cyclohexyl ester **25** in excellent yields. The daily production of **24** and **25** is, respectively, 605 mmol (153 g) and 677 mmol (198 g). It is also possible to use the current reaction conditions in batch to prepare **21**, **23**, and **25** in good yields. Not only are these esters, derived from secondary alcohols, notoriously difficult to prepare by standard esterification processes, but no practical synthetic method is currently available to prepare the corresponding diazo reagents.

Table 5: Continuous-flow esterification of carboxylic acids with amines.



[a] 0.5 M of $TMSCH_2NH_2$, 0.25 M of R^2CO_2H and 0.4 M of $Pr(ONO)_2$ was used. [b] R^1NH_2 was in 2-MeTHF (no MeOH). [c] 0.5 M of RNH_2, 0.1 M of R^2CO_2H and 0.16 M of $Pr(ONO)_2$ was used. [d] The reaction was performed in batch for 20 min at 80 °C (no MeOH). [e] The reaction was performed in CH_2Cl_2.

In conclusion, a novel synthesis of $TMSCHN_2$ by diazotization of $TMSCH_2NH_2$ has been developed in batch and in continuous flow. This new protocol was used to synthesize other silylated diazo reagents. A work-up procedure was devised to produce a 2-MeTHF solution of $TMSCHN_2$ with 99 % purity, and it was successfully used in transition metal catalyzed methylenation and homologation reactions. $TMSCHN_2$ was also used to produce pyrazoles in good to excellent yields. Finally, one-pot esterification processes were also reported, namely a continuous flow reaction which allowed the in situ esterification of carboxylic acids with various amines (including ones for which the diazo reagent is currently not readily available) to produce esters in excellent yields. The process is particularly suitable to prepare esters derived from secondary alcohols.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · diazo compounds · flow chemistry · esterification · synthetic methods

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[1] Seminal discovery: a) M. F. Lappert, J. Lorberth, *Chem. Commun.* **1967**, 836; b) D. Seyferth, A. W. Dow, H. Menzel, T. C. Flood, *J. Am. Chem. Soc.* **1968**, *90*, 1080; c) D. Seyferth, H. Menzel, A. W. Dow, T. C. Flood, *J. Organomet. Chem.* **1972**, *44*, 279; d) T. Aoyama, T. Shioiri, *Tetrahedron Lett.* **1980**, *21*, 4461.

[2] Reviews: a) J. Podlech, *J. Prakt. Chem.* **1998**, *340*, 679; b) T. Shioiri, T. Aoyama, T. Snowden, *Trimethylsilyldiazomethane*, in e-EROS, Encyclopedia of Reagents for Organic Synthesis, DOI: 10.1002/047084289X.rt298, Wiley, Hoboken, **2001**.

[3] According to Scifinder, $\mathrm{TMSCHN_2}$ has been used in over 5000 publications since the year 2000.

[4] a) H. Lebel, V. Paquet, C. Proulx, *Angew. Chem. Int. Ed.* **2001**, *40*, 2887; *Angew. Chem.* **2001**, *113*, 2971; b) H. Lebel, V. Paquet, *J. Am. Chem. Soc.* **2004**, *126*, 320; c) H. Lebel, M. Davi, S. Diez-Gonzalez, S. P. Nolan, *J. Org. Chem.* **2007**, *72*, 144; d) H. Lebel, M. Davi, *Adv. Synth. Catal.* **2008**, *350*, 2352.

[5] This method had proven particularly useful for the methylenation of sensitive aldehydes and ketones. See: a) D. J. Clausen, S. Wan, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2011**, *50*, 5178; *Angew. Chem.* **2011**, *123*, 5284; b) E. C. Cherney, J. C. Green, P. S. Baran, *Angew. Chem. Int. Ed.* **2013**, *52*, 9019; *Angew. Chem.* **2013**, *125*, 9189; c) Y. Akahori, H. Yamakoshi, S. Hashimoto, S. Nakamura, *Org. Lett.* **2014**, *16*, 2054; d) Y. Yang, C. W. Haskins, W. Zhang, P. L. Low, M. Dai, *Angew. Chem. Int. Ed.* **2014**, *53*, 3922; *Angew. Chem.* **2014**, *126*, 4003.

[6] T. Shioiri, T. Aoyama, S. Mori, *Org. Synth.* **1990**, *68*, 1.

[7] Selected reviews: a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688; *Angew. Chem.* **2015**, *127*, 6788; b) S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425; c) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noel, *Chem. Rev.* **2016**, *116*, 10276; d) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892.

[8] Reviews: a) S. T. R. Müller, T. Wirth, *ChemSusChem* **2015**, *8*, 245; b) B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. Eur. J.* **2015**, *21*, 2298; c) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981.

[9] Diazald a) M. Struempel, B. Ondruschka, R. Daute, A. Stark, *Green Chem.* **2008**, *10*, 41; b) R. A. Maurya, C. P. Park, J. H. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2011**, *50*, 5952; *Angew. Chem.* **2011**, *123*, 6074; c) F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *15*, 5590; d) V. D. Pinho, B. Gutmann, L. S. M. Miranda, R. O. M. A. de Souza, C. O. Kappe, *J. Org. Chem.* **2014**, *79*, 1555; e) D. Dallinger, V. D. Pinho, B. Gutmann, C. O. Kappe, *J. Org. Chem.* **2016**, *81*, 5814.

[10] MNU: E. Rossi, P. Woehl, M. Maggini, *Org. Process Res. Dev.* **2012**, *16*, 1146.

[11] Diazo reagents from hydrazones: a) H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *Tetrahedron* **2013**, *69*, 2276; b) N. M. Roda, D. N. Tran, C. Battilocchio, R. Labes, R. J. Ingham, J. M. Hawkins, S. V. Ley, *Org. Biomol. Chem.* **2015**, *13*, 2550; c) É. Lévesque, S. T. Laporte, A. B. Charette, *Angew. Chem. Int. Ed.* **2017**, *56*, 837; *Angew. Chem.* **2017**, *129*, 855.

[12] $\mathrm{TMSCHN_2}$ has never been prepared, either by diazotization or in continuous-flow synthesis. However, a commercially available $\mathrm{TMSCHN_2}$ solution has been used in flow, namely to prepare diazo ketones: see L. J. Martin, A. L. Marzinzik, S. V. Ley, I. R. Baxendale, *Org. Lett.* **2011**, *13*, 320.

[13] a) R. B. Silverman, X. Lu, G. M. Banik, *J. Org. Chem.* **1992**, *57*, 6617; b) A. R. Katritzky, Z. Yang, Q. Hong, *J. Org. Chem.* **1994**, *59*, 5097.

[14] a) A. G. M. Barrett, D. C. Braddock, I. Lenoir, H. Tone, *J. Org. Chem.* **2001**, *66*, 8260; b) R. P. Wurz, A. B. Charette, *Org. Lett.* **2002**, *4*, 4531; c) B. Morandi, A. Dolva, E. M. Carreira, *Org. Lett.* **2012**, *14*, 2162.

[15] a) B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 938; *Angew. Chem.* **2010**, *122*, 950; b) B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 1101; *Angew. Chem.* **2011**, *123*, 1133; c) P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2015**, *54*, 6558; *Angew. Chem.* **2015**, *127*, 6658.

[16] In flow: a) R. A. Maurya, K.-I. Min, D.-P. Kim, *Green Chem.* **2014**, *16*, 116; b) S. T. R. Muller, D. Smith, P. Hellier, T. Wirth, *Synlett* **2014**, 871; c) B. Pieber, C. O. Kappe, *Org. Lett.* **2016**, *18*, 1076; d) L. Mertens, K. J. Hock, R. M. Koenigs, *Chem. Eur. J.* **2016**, *22*, 9542.

[17] $\mathrm{TMSCHN_2}$ is 10000 times more nucleophilic than ethyl diazoacetate, and as nucleophilic as Danishefsky's diene, according to the nucleophilic scale established by Mayr:and co-workers T. Bug, M. Hartnagel, C. Schlierf, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 4068.

[18] a) W. K. Anderson, A. S. Milowsky, *J. Med. Chem.* **1986**, *29*, 2241; b) M. Letellier, D. J. McPhee, D. Griller, *Synth. Commun.* **1988**, *18*, 1975.

[19] See the Supporting Information for details.

[20] D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675.

[21] For batch one-pot diazo formation from hydrazone-esterification, see: a) M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc.* **2004**, *126*, 12222; b) R. A. Squitieri, G. P. Shearn-Nance, J. E. Hein, J. T. Shaw, *J. Org. Chem.* **2016**, *81*, 5278.

[22] In contrast, previously reported diazomethane esterification in continuous flow were all based on the generation of diazomethane (with possible build-up of the reagent), followed by the addition of the carboxylic acid; see References [9,10].

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Communications

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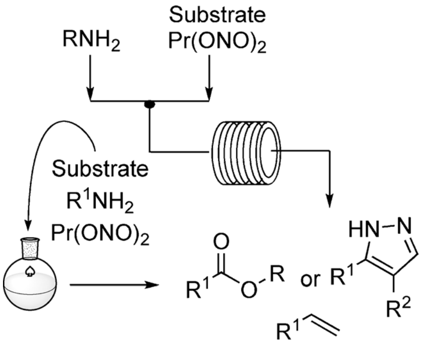

Diazo made easy: The diazotization of various amines, namely TMSCH$_2$NH$_2$ to produce TMSCHN$_2$, is reported using batch and continuous-flow synthesis. One-pot esterification and 1,3-dipolar cycloaddition processes are disclosed. The esterification process combines the in situ formation of the diazo reagent and its immediate consumption by the substrate, a process which is particularly suitable for the preparation of esters from secondary amines.