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Communication

Brönsted acid catalyzed addition of N^1-*p*-methyl toluenesulfonyl triazole to olefins for the preparation of N^2-alkyl 1,2,3-triazoles with high N^2-selectivity

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ABSTRACT

An efficient new method has been developed to synthesize N^2-alkyl 1,2,3-triazole products by toluenesulfonic acid (TsOH) catalyzed addition of N^1-Ts substituted 1,2,3-triazoles to olefins. The reactions of monosubstituted and unsubstituted triazole substrates with various olefins, including vinyl esters, are explored.

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N-Substituted 1,2,3-triazoles have aroused considerable research interests in recent years and have widespread applications in biological science [1–4], material chemistry [5–9] and medicinal chemistry [10–13]. N^1-substituted 1,2,3-triazoles could be prepared either by a thermo- or by metal-mediated [14–17] (Cu(I)-catalyzed for 1,4-disubstituted [15,18–20] and Ru(II)-catalyzed for 1,5-disubstituted [21,22]) 1,3-dipolar cycloaddition reaction, whereas the synthesis of N^2-substituted 1,2,3-triazoles has been far less explored to date. Many recent efforts have been made to prepare N^2-aryl [23–25] and N^2-allyl [26–29] 1,2,3-triazoles with high N^2-selectivity through a palladium catalyzed coupling reaction by using suitable bulky phosphine ligands [25,29]. However, N^2-alkyl-1,2,3-triazoles can only be obtained by the conversion of non-substituted *NH*-triazoles with appropriate electrophiles through nucleophilic substitution [30–33].

Recently, some researchers reported the synthesis of N^2-alkyl 1,2,3-triazoles through the nucleophilic reaction of alkyl halides with bulky C-4- and C-5-disubstituted *NH*-1,2,3-triazoles [30–32], in which, the synthetic utilities were therefore restricted by the substrate's steric requirements (Scheme 1, Eq. (1)). A general, simple and scalable method for the synthesis of the N^2-alkyl 1,2,3-triazoles, especially for 4-monosubstituted or 4,5-unsubstituted 1,2,3-triazoles is still not available. In the course of our research on triazole chemistry [34,35], we were wondering if N^2-substituted triazoles could be synthesized from their N^1-substituted isomers with the incorporation of labile N^1-substitutents (Scheme

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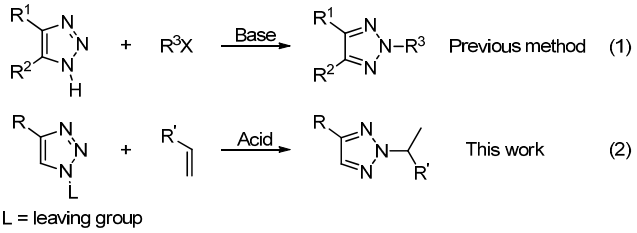


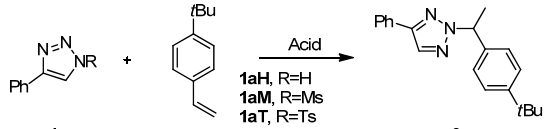
Scheme 1. Nucleophilic reaction of the bulky *NH*-1,2,3-triazole or N^1-substituted 1,2,3-triazole to provide N^2-substituted 1,2,3-triazole.

1, Eq. (2)). Because the preparation of N^1-substituted 1,2,3-triazoles has been well documented in previous research, we envisioned that this new strategy would be flexible and improve the ability to construct N^2-susbstituted 1,2,3-triazoles.

Brönsted acid-mediated alkene addition is one of the basic organic transformations in synthetic chemistry, and has been widely utilized for the functionalization of olefins. However, the addition of *NH*-1,2,3-triazole to olefins has been seldom explored before except an example of michael addition of *NH*-1,2,3-triazole onto α,β-unsaturated ester to provide N^1-alkyl triazole products [36]. Herein, we report the synthesis of N^2-alkyl 1,2,3-triazole with high N^2-selectivity through acid mediated addition of *NH*-1,2,3-triazole to olefins.

In a preliminary trial, N^1-substituted 1,2,3-triazole **1a** with different substitution patterns was chosen as the substrate for our initial investigation. As shown in Table 1, the reaction of **1aH** (R=H) with 4-tertbutyl styrene **2a** in the presence of 1 equivalent of toluenesulfonic acid (TsOH) in CH_2Cl_2 gave no desired transformation at room temperature (Table 1, entry 1). However, when the reaction temperature was increased to 65 °C in chloroform, the desired N^2-substituted coupling adduct **3a**

Table 1
Brönsted acid catalyzed N^2-selective addition of *NH*-1,2,3-triazole **1a** to 4-tertbutyl styrene **2a**.



Entry	R	Acid (Equiv.)	**1a/2a**	Yield [b] (%)
1[a]	H	TsOH(1)	1/2	0
2	H	TsOH(1)	1/2	30
3	Ms	TsOH(1)	1/2	24
4	Ts	TsOH(1)	1/2	47
5	1,1-dimethyl benzyl	TsOH(1)	1/2	<5%
6	Ts	TfOH(1)	1/2	Trace
7	Ts	Con. HCl(1)	1/2	<5%
8	Ts	HOAc (1)	1/2	ND
9	Ts	TsOH(1)	1/4	54
10	Ts	TsOH(1)	1/6	77
11	Ts	TsOH(1)	1/8	74
12	Ts	TsOH(2)	1/6	80
13	Ts	$BF_3{\cdot}Et_2O$	1/6	ND
14	Ts	$AuCl_3$	1/6	Trace

Reactions conditions: 0.1 mmol scale, solvent $CHCl_3$ 2 mL, 65 °C.
[a] Room temperature, solvent CH_2Cl_2. [b] Isolated yield.

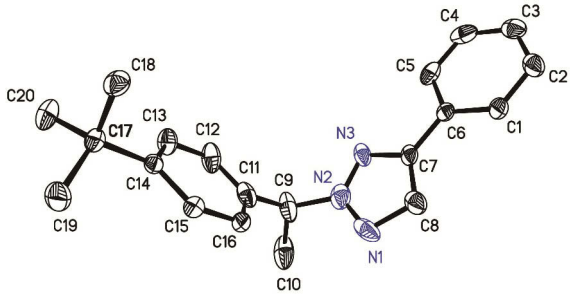
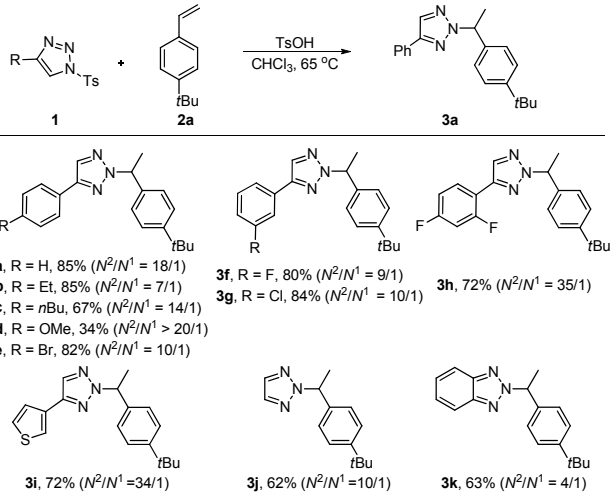


Fig. 1. ORTEP picture of compound **3a** with the displacement ellipsoid drawn at 30% probability.

was obtained in 30% yield with N^2/N^1 = 3/1. The structure of **3a** was confirmed by X-ray chromatography, as shown in Fig. 1, which shows that the triazole group connects with the alkyl group at the *N*-2 nitrogen atom. In previously reported examples, including acetylation [37], Michael addition [38] and S_N2 substitution reaction for the conversion of unsubstituted *NH*-triazoles [9], the N^1-substituted triazoles were usually the dominant products. Therefore, this result was very interesting. Various R substituents were then evaluated (Table 1, entries 3–5), in which the toluenesulfonyl (Ts) group performed much better than the other counterparts. The labile 1,1-dimethylbenzyl group gave only a trace amount of **3a**. Other Brönsted acid catalysts were also tested. It was found that TsOH performed much better than CF_3SO_3H, concentrated HCl and CH_3COOH (Table 1, entries 6–8). Increasing the equivalents of **2a** and TsOH enhanced the yield of **3a** (Table 1, entries 9–12). In the control experiments, the Lewis acid $BF_3{\cdot}Et_2O$ and the metal catalyst $AuCl_3$ gave no desired transformation (Table 1, entries 13 and 14).

With the optimized reaction conditions in hand (Table 1, entry 12), we then examined the scope of this transformation by synthesizing a variety of N^2-alkyl 1,2,3- triazole derivatives. As shown in Table 2, a series of 1,2,3-triazole substrates were

Table 2
TsOH mediated N^2-selective addition of various *NH*-1,2,3-triazoles to 4-tertbutyl styrene **2a**.



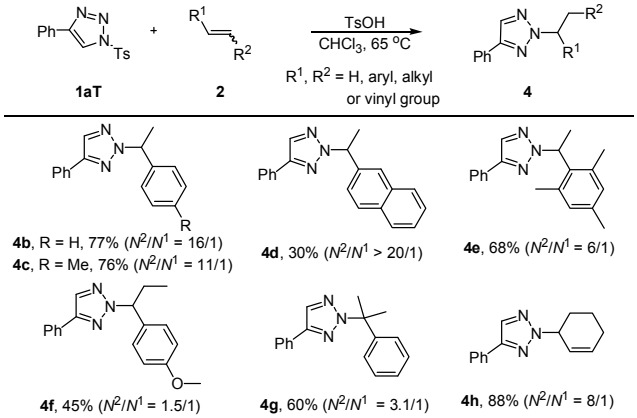
Reaction conditions: 0.1 mmol scale, $CHCl_3$ 2 mL, 65 °C, **1/2a** = 1:6, TsOH 2 equiv.

examined by using 4-tertbutyl styrene **2a** as the coupling partner. At first, several phenyl triazoles with different substitution patterns were tested, in which substrates with electron-rich substituents (Table 2, **3a–c**) performed better than their electron-poor counterparts (Table 2, **3e–h**). *p*-Methoxy phenyl triazole **1d** gave **3d** in only 34% yield (Table 2, **3d**). The reaction of thiophenyl triazole **1i** went smoothly, affording **3i** in moderate yields with a high N^2-selectivity. Unsubstituted *NH*-1,2,3-triazole **1j** worked very well, providing **3j** in moderate yield with a good N^2-selectivity. Notably, the benzotriazole coupling adduct **3k** was obtained with good N^2-selectivity (N^2/N^1 = 4/1). Compared with the low N^2-selectivities obtained in previous reports, this result significantly improves the potential application of the acid mediated reaction [21,22]. Because of its instability, the N^1-Ts alkyl substrates were not explored.

The TsOH mediated reaction of **1aT** with a variety of olefins was explored, wherein, aromatic olefins and diene substrates worked very well. As shown in Table 3, N^2-alkyl 1,2,3-triazoles **4b** and **4c** were obtained in good yields with high N^2-selectivities from the reactions of substituted styrene **2b** and **2c**. In the reactions of the bulky 2-vinylnaphthalene and 2,4,6-trimethyl styrene, the substrate's steric hindrance affected the yields of **4d** and **4e** (Table 3, **4d** and **4e**). Moreover, a low N^2/N^1-selectivity was observed in the **4f** (Table 3, **4f**). This might be because of the formation of a stabilized carbon cation intermediate. Similarly, trisubstituted olefin **2g**, which would lead to a stabilized trisubstituted carbon cation intermediate, gave **4g** with a low N^2-selectivity (N^2/N^1 = 3.1/1). Cyclohexadiene was also tested, providing **4h** in 88% yield with a N^2/N^1 = 8/1. The reactions of the aliphatic olefins were unsuccessful, owing to the poor regioselectivity of the olefins.

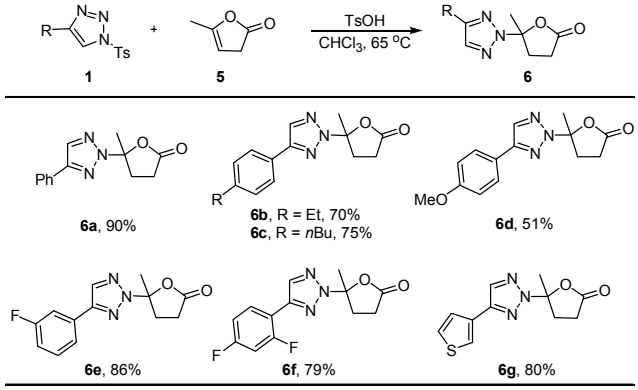
Next, we explored the TsOH mediated reactions of vinyl ester **5**. As shown in Table 4, a series of N^2-substituted 1,2,3-triazole derivatives were obtained in moderate to good yields. Notably, only N^2-isomers were obtained in these reactions. No obvious electronic effect or site preference was observed, and the N^2-substituted *p*-methoxy phenyl triazole **6d** was obtained in a low yield. The structure of **6f** was determined by X-ray chromatography, as shown in Fig. 2.

Table 3
TsOH mediated N^2-selective addition of *NH*-1,2,3-triazole **1aT** to various olefin **2**.



Reaction conditions: 0.1 mmol scale, $CHCl_3$ 2 mL, 65 °C, **1aT/2** = 1/6, TsOH 2 equiv.

Table 4
TsOH mediated N^2-selective addition of various *NH*-1,2,3-triazole **1** to vinyl ester **5**.



Reaction conditions: 0.1 mmol scale, $CHCl_3$ 2 mL, 65 °C, **1/5** = 1:6, TsOH 2 equiv.

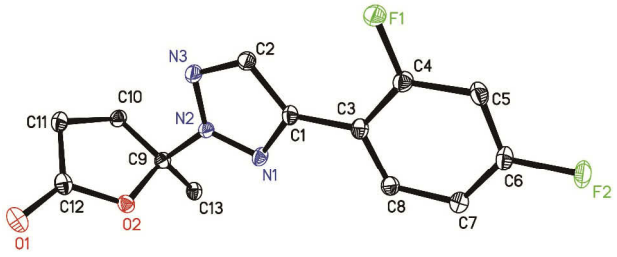
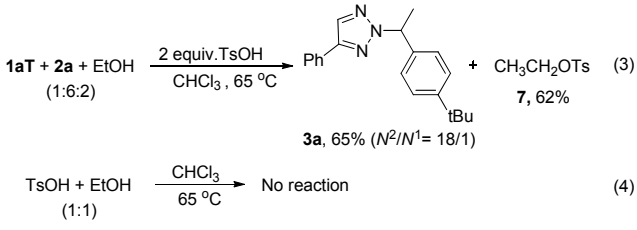


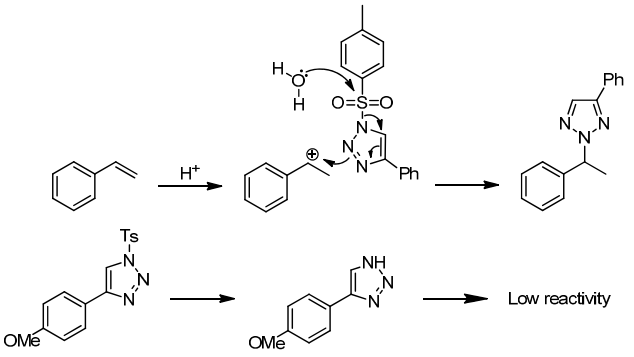
Fig. 2. ORTEP picture of compound **6f** with the displacement ellipsoid drawn at 30% probability.

As depicted in Eq. (2) in Scheme 1, the Ts protecting group in the N^1-Ts triazole substrates would act as the leaving group, which should be trapped by the trace amount of water in $CHCl_3$. To elucidate the detailed reaction mechanism, two equivalents of ethanol were added in the reaction of **1a** and **2a** (Scheme 2, Eq. (3)). It was found that the desired N^2-coupling adduct **3a** was obtained in 65% yield, together with the formation of CH_3CH_2OTs **7** in 62% yield. The reaction of TsOH with ethanol was performed in $CHCl_3$ at 65 °C as the control experiment (Scheme 2, Eq. (4)), in which no *p*-toluenesulfonyl ester **7** was detected.

A plausible mechanism was then proposed based on these observations. As shown in Scheme 3, a carbon cation intermediate is generated from the styrene with the addition of a proton, which is then attacked by the internal nitrogen of the N^1-Ts triazole substrate to give the desired N^2-alkyl 1,2,3-triazole product. At the same time, the leaving Ts group is trapped by



Scheme 2. Trapping the leaving Ts group with ethanol.



Scheme 3. A plausible mechanism for the acid-mediated substitution reaction of N^1-Ts triazole with olefins.

the trace amount of water in $CHCl_3$ to give TsOH as the side product. The low reactivity of 1-(*p*-methoxyphenyl) triazole can be rationalized by the instability of its Ts protection group under the reaction conditions (**3d** in Table 2, **6d** in Table 4). The low N^2/N^1 selectivities of **4f** and **4g** can be explained by the reversible elimination of these N^2-alkyl triazole products, owing to the improved stability of the corresponding carbon cation intermediates.

In summary, a new efficient method was developed to synthesize N^2-alkyl 1,2,3-triazole products through the TsOH catalyzed addition of N^1-Ts substituted 1,2,3-triazoles to olefins. Monosubstituted and unsubstituted triazole substrates and various olefins, including vinyl esters, worked very well in this reaction. Considering the easy availability of N^1-substituted 1,2,3-triazoles using the previously reported methods, the reaction reported in this paper provides a simple method to construct various types of N^2-substituted triazoles.

References

[1] M. E. Hahn, T. W. Muir, *Trends Biochem. Sci.,* **2005**, 30, 26–34.
[2] W. P. Heal, S. R. Wickramasinghe, R. J. Leatherbarrow, E. W. Tate, *Org. Biomol. Chem.,* **2008**, 6, 2308–2315.
[3] P. Schmieder, R. Kuhne, J. Rademann, *Angew. Chem. Int. Ed.,* **2009**, 48, 5042–5045.
[4] G. Schneider, *Nat. Rev. Drug Discov.,* **2010**, 9, 273–276.
[5] H. M. Li, F. Y. Cheng, A. M. Duft, A. Adronov, *J. Am. Chem. Soc.,* **2005**, 127, 14518–14524.
[6] D. I. Rozkiewicz, D. Janczewski, W. Verboom, B. J. Ravoo, D. N. Reinhoudt, *Angew. Chem. Int. Ed.,* **2006**, 45, 5292–5296.
[7] M. Wyszogrodzka, R. Haag, *Chem. Eur. J.,* **2008**, 14, 9202–9214.
[8] T. Gadzikwa, O. K. Farha, C. D. Malliakas, M. G. Kanatzidis, J. T. Hupp, S. T. Nguyen, *J. Am. Chem. Soc.,* **2009**, 131, 13613–13615.
[9] P. L. Golas, K. Matyjaszewski, *Chem. Soc. Rev.,* **2010,** 39, 1338–1354.
[10] Y. M. Chabre, R. Roy, *Curr. Top. Med. Chem.,* **2008**, 8, 1237–1285.
[11] M. Colombo, I. Peretto, *Drug Discov. Today,* **2008**, 13, 677–684.
[12] R. Hanselmann, G. E. Job, G. Johnson, R. L. Lou, J. G. Martynow, M. M. Reeve, *Org. Process Res. Dev.*, **2010**, 14, 152–158.
[13] R. Moumne, V. Larue, B. Seijo, T. Lecourt, L. Micouin, C. Tisne, *Org. Biomol. Chem.,* **2010**, 8, 1154–1159.
[14] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.,* **2002**, 41, 2596–2599.
[15] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.,* **2001**, 40, 2004–2021.
[16] J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.,* **2007**, 36, 1249–1262.
[17] P. Wu, V. V. Fokin, *Aldrichim. Acta,* **2007**, 40, 7–17.
[18] R. Huisgen, in: A. Padwa ed., *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, **1984**.
[19] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.,* **2002**, 41, 2596–2599.
[20] M. M. Majireck, S. M. Weinreb, *J. Org. Chem.,* **2006**, 71, 8680–8683.
[21] L. Zhang, X. G. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. C. Jia, *J. Am. Chem. Soc.,* **2005**, 127, 15998–15999.
[22] L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett.,* **2007**, 9, 5337–5339.
[23] Y. X. Liu, W. M. Yan, Y. F. Chen, J. L. Petersen, X. D. Shi, *Org. Lett.,* **2008**, 10, 5389–5392.
[24] X. J. Wang, L. Zhang, H. Lee, N. Haddad, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.,* **2009**, 11, 5026–5028.
[25] S. Ueda, M. J. Su, S. L. Buchwald, *Angew. Chem. Int. Ed.,* **2011**, 50, 8944–8947.
[26] S. Kamijo, T. N. Jin, Z. B. Huo, Y. Yamamoto, *J. Am. Chem. Soc.,* **2003**, 125, 7786–7787.
[27] S. Kamijo, T. N. Jin, Z. B. Huo, Y. Yamamoto, *J. Org. Chem.,* **2004**, 69, 2386–2393.
[28] W. M. Yan, Q. Y. Wang, Y. F. Chen, J. L. Petersen, X. D. Shi, *Org. Lett.,* **2010**, 12, 3308–3311.

Graphical Abstract

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Brönsted acid catalyzed addition of N^1-*p*-methyl toluenesulfonyl triazole to olefins for the preparation of N^2-alkyl 1,2,3-triazoles with high N^2-selectivity

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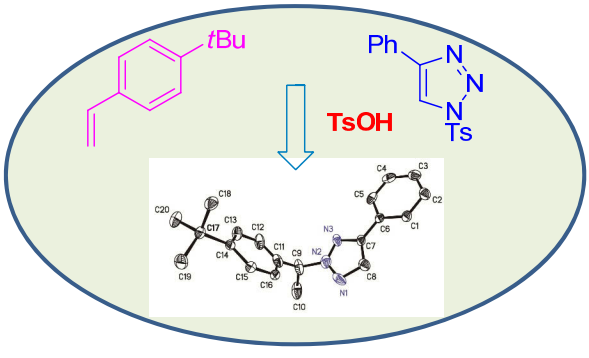

An efficient new method has been developed to synthesize N^2-alkyl 1,2,3-triazole products though the TsOH catalyzed addition of N^1-Ts substituted 1,2,3-triazoles to olefins.

[29] K. Xu, N. Thieme, B. Breit, *Angew. Chem. Int. Ed.,* **2014**, 53, 7268–7271.
[30] Y. F. Chen, Y. X. Liu, J. L. Petersen, X. D. Shi, *Chem. Commun.,* **2008**, 3254–3256.
[31] X. J. Wang, K. Sidhu, L. Zhang, S. Campbell, N. Haddad, D. C. Reeves, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.,* **2009**, 11, 5490–5493.
[32] X. J. Wang, L. Zhang, D. Krishnamurthy, C. H. Senanayake, P. Wipf, *Org. Lett.,* **2010**, 12, 4632–4635.
[33] J. Kalisiak, K. B. Sharpless, V. V. Fokin, *Org. Lett.,* **2008**, 10, 3171–3174.
[34] J. Wen, L. L. Zhu, Q. W. Bi, Z. Q. Shen, X. X. Li, Z. Wang, Z. L. Chen, *Chem. Eur. J.,* **2014**, 20, 974–978.
[35] L. L. Zhu, X. Q. Xu, J. W. Shi, B. L. Chen, Z. L. Chen, *J. Org. Chem.,* **2016**, 10.1021/acs.joc.6b00185.
[36] H. Gold, *Justus Liebigs Annalen der Chemie*, **1965**, 688, 205–216.
[37] A. R. Katritzky, A. Pastor, *J. Org. Chem.*, **2000**, 65, 3679–3682.
[38] J. Wang, H. Li, L. S. Zu, W. Wang, *Org. Lett.*, **2006**, 8, 1391–1394.