



Dy(OTf)₃-mediated selective substitution of *N*-(α -benzotriazolyl-alkyl)amides with active methylene compounds for synthesis of benzotriazole derivatives

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ABSTRACT

A Dy(OTf)₃-mediated selective substitution reaction of *N*-(α -benzotriazolyl-alkyl)amides with active methylene compounds is reported. The present procedure provides a facile method for the synthesis of benzotriazole derivatives.

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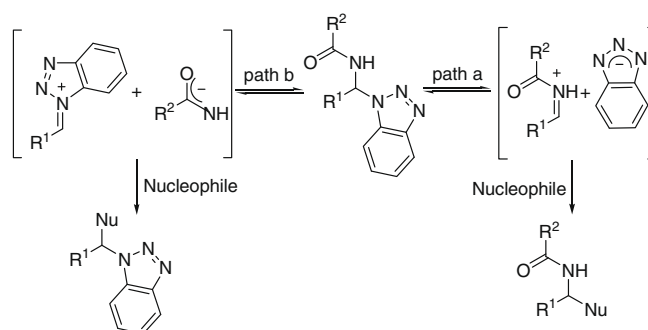
N-(α -Benzotriazolyl-alkyl)amides, developed by the Katritzky group, have been used advantageously as the key intermediates in organic synthesis.¹ As an alternative method to the Mannich reaction, they can react with various nucleophiles,^{2,3} such as active methylene and methine compounds,^{2d,3f} alkyl vinyl ethers, silyl enol ethers, enamines,^{2k} propen-2-yl acetate,^{2f} enolizable aldehydes,^{2m} and allylsamarium bromide,^{3e} to afford a variety of useful compounds. *N*-(α -Benzotriazolyl-alkyl)amides have a bifunctional structure (X–C–Y), in which two different leaving groups attach to the same carbon. The high reactivity of *N*-(α -benzotriazolyl-alkyl)amides in amidoalkylation reactions owes mainly to the good leaving ability of the benzotriazolyl moiety (Scheme 1, path a). The selective elimination of the amide moiety (Scheme 1, path b),⁴ which provides a versatile method for the synthesis of benzotriazole derivatives,⁵ has received much less scrutiny.

We envisioned that the selective elimination of the two leaving groups might be achieved by the proper choice of a Lewis acid and the reaction conditions. In addition, it is desirable that the subsequent nucleophilic addition can be promoted by the Lewis acid without isolation of the unstable imine intermediate.⁶ To verify our hypothesis, a set of experiments were carried out using benzotriazolyl-substituted amide **1a** and diethyl malonate as model substrates. The expected product **2a** was reported to have fungicidal activities against *glomerella gossypii* and *penicillium italicum*.⁷

The preliminary survey, carried out in THF at 65 °C, allowed us to evaluate the catalytic efficiency of various Lewis acids (Table 1). Gratifyingly, in an initial experiment, we observed the formation of desired product **2a** when the reaction was catalyzed by FeCl₃ (Table 1, entry 1). Further investigation revealed that Dy(OTf)₃ was the best catalyst for the generation of **2a** (Table 1, entry 18), while inferior results were displayed in the presence of other Lewis acids (Table 1, entries 2–17). The major byproducts of the reaction were the normal amidoalkylation products, benzyl aldehyde and benz-

amide. These were assumed to be generated from the reaction via path a. The structure of **2a** was confirmed by spectral methods and the single-crystal diffraction analysis (Fig. 1).

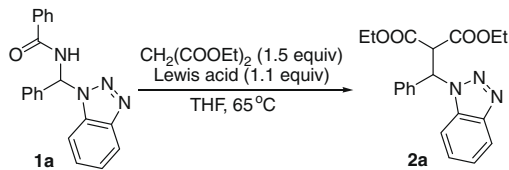
Motivated by the synthetic potential of the possible method, the reaction was further optimized by examining various reaction conditions, and some of the results are shown in Table 2. An increase in the amount of Dy(OTf)₃ did not improve the yield of **2a**, while the reaction could not be completed with the use of 0.5 equivalents of Dy(OTf)₃ (Table 1, entries 2 and 3). No product **2a** was detected when EtOH, *t*-BuOH, 1,4-dioxane, and EtOAc were used as the solvent, while the reaction could proceed in THF, ClCH₂CH₂Cl₂, and toluene with varied efficiency (Table 1, entries 4–11). A higher temperature resulted in a complicated reaction and a lower yield of **2a**, while no reaction occurred at a lower temperature (Table 1, entries 12 and 13). When Et₃N and *t*-BuOK were introduced into the reaction, complex reactions were observed, and no product **2a** was obtained (Table 1, entries 14 and 15). We were delighted to find that the reaction was promoted and the yield of **2a** was improved to 68% when 1 equiv of benzotriazole was utilized as the additive (Table 1, entry 16). When the reaction was conducted in THF, product **2a** was isolated in 78% yield (Table 1, entry 18).



Scheme 1. The selective substitution reaction of *N*-(α -benzotriazolyl-alkyl)amide.

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Table 1
Evaluation of various Lewis acids^a


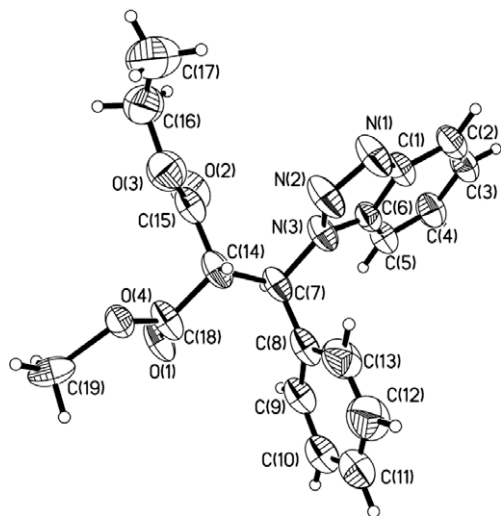
Entry	Lewis acid	2a ^b (%)
1	FeCl ₃	25
2	FeCl ₂	Trace
3	Fe(acac) ₃	Trace
4	BF ₃ ·Et ₂ O	0
5	InCl ₃	0
6	BiCl ₃	10
7	YbCl ₃	Trace
8	PdCl ₂	0
9	ZnCl ₂	0
10	CuBr	0
11	Pd(OAc) ₂	0
12	Bi(OTf) ₃	0
13	Zn(OTf) ₂	0
14	Cu(OTf) ₂	0
15	Yb(OTf) ₃	Trace
16	Sc(OTf) ₃	Trace
17	AgOTf	Trace
18	Dy(OTf) ₃	51

^a The reactions were performed with **1a** (0.5 mmol), diethyl malonate (0.75 mmol), Lewis acid (0.55 mmol) in anhydrous THF (2 mL) at 65 °C.

^b Isolated yields.

The scope of the present reaction was then investigated under the established conditions.⁸ A moderate electronic substrate effect was observed. The reactions of electron-poor substrates afforded the corresponding products in better yields than those of electron-rich substrates (Table 3, entries 1–12). Aliphatic substrates were unreactive under the same conditions (Table 3, entries 13 and 14). Moreover, the reactions with methyl or ethyl 3-oxobutanoate also gave the products **2r** and **2s** in good yields (Table 3, entries 15 and 16). No corresponding products were obtained when 2,4-pentanedione, ethyl 2-nitroacetate, and ethyl 2-cyanoacetate were employed (Table 3, entries 17–19).

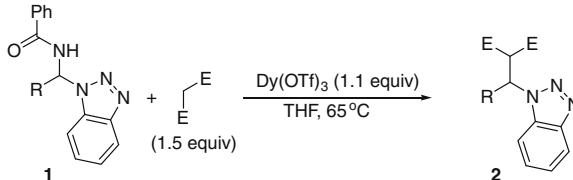
In conclusion, we report here a Dy(OTf)₃-mediated selective substitution reaction of *N*-(α-benzotriazolyl-alkyl)amides with

**Figure 1.** The ORTEP diagram of **2a**.**Table 2**
Optimization of the reaction conditions^a

Entry	Dy(OTf) ₃ (equiv)	Solvent	Temperature (°C)	Additive (equiv)	2a ^b (%)
1	1.1	THF	65		51
2	2	THF	65		49
3	0.5	THF	65		34
4	1.1	ClCH ₂ CH ₂ Cl	65		37
5	1.1	CH ₂ Cl ₂	40		0
6	1.1	CH ₃ CN	65		11
7	1.1	EtOH	65		0
8	1.1	<i>t</i> -BuOH	65		0
9	1.1	1,4-Dioxane	65		0
10	1.1	EtOAc	65		0
11	1.1	Toluene	65		49
12	1.1	Toluene	80		39
13	1.1	Toluene	50		0
14	1.1	Toluene	65	(1) Et ₃ N	0
15	1.1	Toluene	65	(1) <i>t</i> -BuOK	0
16	1.1	Toluene	65	(1) Benzotriazole	68
17	1.1	Toluene	65	(2) Benzotriazole	67
18	1.1	THF	65	(1) Benzotriazole	78

^a The reactions were performed with **1a** (0.5 mmol), diethyl malonate (0.75 mmol) in anhydrous solvent (2 mL).

^b Isolated yields.

Table 3
Extending of substrate scope^a


Entry	R	CH ₂ E ₂	2 ^b (%)
1	C ₆ H ₅	CH ₂ (COOEt) ₂	2a (78)
2	4-NO ₂ -C ₆ H ₄	CH ₂ (COOEt) ₂	2b (78)
3	4-Cl-C ₆ H ₄	CH ₂ (COOEt) ₂	2c (66)
4	2-Cl-C ₆ H ₄	CH ₂ (COOEt) ₂	2d (71)
5	2,4-Di-Cl-C ₆ H ₃	CH ₂ (COOEt) ₂	2e (76)
6	2-Br-C ₆ H ₄	CH ₂ (COOEt) ₂	2f (70)
7	2-Br-5-F-C ₆ H ₃	CH ₂ (COOEt) ₂	2g (66)
8	4-CH ₃ -C ₆ H ₄	CH ₂ (COOEt) ₂	2h (63)
9	4-CH ₃ O-C ₆ H ₄	CH ₂ (COOEt) ₂	2i (58)
10	4-PhCH ₂ O-C ₆ H ₄	CH ₂ (COOEt) ₂	2j (70)
11	3-PhCH ₂ O-C ₆ H ₄	CH ₂ (COOEt) ₂	2k (74)
12	3-CH ₃ O-4-PhCH ₂ O-C ₆ H ₃	CH ₂ (COOEt) ₂	2l (40)
13	<i>n</i> -Pr	CH ₂ (COOEt) ₂	2p (0)
14	<i>t</i> -Bu	CH ₂ (COOEt) ₂	2q (0)
15	C ₆ H ₅	CH ₃ COCH ₂ COOCH ₃	2r (83)
16	C ₆ H ₅	CH ₃ COCH ₂ COOEt	2s (69)
17	C ₆ H ₅	CH ₃ COCH ₂ COCH ₃	2t (0)
18	C ₆ H ₅	NO ₂ CH ₂ COOEt	2u (0)
19	C ₆ H ₅	CNCH ₂ COOEt	2v (0)

^a The reactions were performed with **1** (0.5 mmol), CH₂E₂ (0.75 mmol), Dy(OTf)₃ (0.55 mmol) in anhydrous THF (2 mL) at 65 °C.

^b Isolated yields.

active methylene compounds. The present procedure will provide a facile method for the synthesis of benzotriazole derivatives. Further studies on the scope, mechanism, and the application of this system are ongoing and will be reported in due course.

Acknowledgments

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References and notes

- For selected reviews, see: (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, 47, 2683; (b) Katritzky, A. R.; Yang, Z.; Cundy, D. J. *Aldrichim. Acta* **1994**, 27, 31; (c) Katritzky, A. R.; Lan, X. *Chem. Soc. Rev.* **1994**, 363; (d) Katritzky, A. R.; Lan, X.; Fan, W. Q. *Synthesis* **1994**, 445; (e) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, 98, 409.
- (a) Katritzky, A. R.; Bachwal, S.; Caster, K. C.; Mahni, F.; Law, K. W.; Rubio, O. J. *Chem. Soc., Perkin Trans. 1* **1987**, 791; (b) Katritzky, A. R.; Drewniak, M. J. *Chem. Soc., Perkin Trans. 1* **1988**, 2339; (c) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Synthesis* **1991**, 69; (d) Katritzky, A. R.; Pernak, J.; Fan, W. Q.; Saczewski, F. J. *Org. Chem.* **1991**, 56, 4439; (e) Katritzky, A. R.; Fan, W.; Black, M.; Pernak, J. J. *Org. Chem.* **1992**, 57, 541; (f) Katritzky, A. R.; Ignatchenko, A. V.; Lang, H. J. *Org. Chem.* **1995**, 60, 4002; (g) Katritzky, A. R.; Qi, M.; Feng, D. M.; Nichols, D. A. J. *Org. Chem.* **1997**, 62, 4121; (h) Katritzky, A. R.; Li, J. J. *Org. Chem.* **1997**, 62, 238; (i) Katritzky, A. R.; Oniciu, D. D.; Ghiviriga, I. *Synth. Commun.* **1997**, 27, 907; (j) Katritzky, A. R.; Cheng, D.; Henderson, S. A.; Li, J. J. *Org. Chem.* **1998**, 63, 6704; (k) Katritzky, A. R.; Pastor, A.; Voronkov, M. V. J. *Heterocycl. Chem.* **1999**, 36, 777; (l) Katritzky, A. R.; Fang, Y.; Silina, A. J. *Org. Chem.* **1999**, 64, 7622; (m) Katritzky, A. R.; Denisko, O. V.; Busont, S. J. *Org. Chem.* **2000**, 65, 8066; (n) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, 61, 2555; (o) Katritzky, A. R.; Abdel-Fattah, A. A.; Idzik, K. R.; El-Gendy, B. E.-D. M.; Soloduchko, J. *Tetrahedron* **2007**, 63, 6477.
- (a) Aurrecoechea, J. M.; Fernandez-Acebes, A. *Tetrahedron Lett.* **1992**, 33, 4763; (b) Fernandez-Acebes, A.; Aurrecoechea *Tetrahedron Lett.* **1993**, 34, 549; (c) Wang, X.; Liu, Y.; Zhang, Y. *Tetrahedron* **2003**, 59, 8257; (d) Gizecki, P.; Dhal, R.; Poulard, C.; Gosselin, P.; Dujardin, G. J. *Org. Chem.* **2003**, 68, 4338; (e) Wang, X.; Li, J.; Zhang, Y. *Synth. Commun.* **2003**, 33, 3575; (f) Wang, X.; Mao, H.; Yu, Y.; Zhu, X.; Zhu, C. *Synth. Commun.* **2007**, 37, 3751.
- Wang, X.; Mao, H.; Xie, G.; Du, J. *Synth. Commun.* **2008**, 38, 2908.
- (a) Forsyth, S. A.; MacFarlane, D. R. J. *Mater. Chem.* **2003**, 13, 2451; (b) Kinzel, O.; Fattori, D.; Muraglia, E.; Gallinari, P.; Nardi, M. C.; Paolini, C.; Roscilli, G.; Toniatti, C.; Gonzalez Paz, O.; Laufer, R.; Lahm, A.; Tramontano, A.; Cortese, R.; De Francesco, R.; Ciliberto, G.; Koch, U. J. *Med. Chem.* **2006**, 49, 5404; (c) Wentland, M. P.; Lu, Q.; Ganorkar, R.; Zhang, S.-Z.; Jo, S.; Dana, J.; Cohen, D. J.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2009**, 19, 365.
- (a) Fan, R.; Pu, D.; Qin, L.; Wen, F.; Yao, G.; Wu, J. J. *Org. Chem.* **2007**, 72, 3149; (b) Fan, R.; Wang, W.; Pu, D.; Wu, J. J. *Org. Chem.* **2007**, 72, 5905; (c) Fan, R.; Pu, D.; Wen, F.; Ye, Y.; Wang, X. J. *Org. Chem.* **2008**, 73, 3623.
- Cheng, F.; Wang, H. *Chin. J. Appl. Chem.* **1989**, 6, 38.
- General experimental procedure and spectroscopic data for **2a**: A solution of *N*-(α -benzotriazolyl-alkyl)amide **1** (0.5 mmol) and CH₂E₂ (0.75 mmol) in anhydrous THF (2 mL) was treated with Dy(OTf)₃ (309 mg, 0.55 mmol) and benzotriazole (60 mg, 0.5 mmol). The resulted mixture was stirred at 65 °C. After substrate disappeared (determined by TLC), the mixture was quenched with saturated NaHCO₃, and extracted by ethyl acetate (25 mL \times 3). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20–30% ethyl acetate in hexane) to provide the desired product. *Diethyl 2-((1H-benzo[d][1,2,3]triazol-1-yl)(phenyl)methyl)malonate*:⁷ ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.58–7.50 (m, 3H), 7.34–7.27 (m, 5H), 6.38 (d, *J* = 11.4 Hz, 1H), 5.17 (d, *J* = 11.4 Hz, 1H), 4.10–3.97 (m, 4H), 1.07 (t, *J* = 7.3 Hz, 3H), 1.01 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 166.1, 145.9, 135.4, 132.9, 129.2, 128.9, 128.0, 127.6, 124.2, 119.9, 109.7, 62.2, 62.1, 61.6, 57.2, 13.8, 13.7.