Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6285–6288

Halogen effects in Robinson–Gabriel type reaction of cyclopropanecarboxylic acid *N*′-substituted-hydrazides with PPh_3/CX_4

Yong-Hua Yang and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Received 2 June 2005; revised 11 July 2005; accepted 12 July 2005
Available online 28 July 2005

Abstract—We found that the reaction of cyclopropanecarboxylic acid *N*′-substituted-hydrazides with PPh_3/CCl_4 proceeded smoothly to give the corresponding normal Robinson–Gabriel type product 2-cyclopropyl-5-substituted-[1,3,4]-oxadiazoles in good yields. Using CBr_4 or CI_4 instead of CCl_4 in the above system, the ring opening of cyclopropane occurred after dehydration to give the corresponding 2-(3-halopropyl)-5-substituted-[1,3,4]-oxadiazoles (**4** or **5**) in good yields.

Substituted 1,3,4-oxadiazoles have received intensive interest due to their biological activities and wide use in medicine and agriculture.[1] In addition, these heterocyclic compounds have been used as dye stuffs, UV absorbing and fluorescent materials, and heat-resistant polymers.[2] 1,3,4-Oxadiazoles are generally obtained by Robinson–Gabriel type reaction, an intramolecular dehydration, of *N*,*N*′-disubstituted hydrazines with dehydration agents.[2d,3]

It is well known that triphenylphosphine in the combination with a tetrahalomethane provides reagents that have manifold uses and are finding increasing application in preparative chemistry for halogenation, dehydration, and P–N linking reactions.[4] Of more general importance is tertiary phosphane/tetrachloromethane system, as chlorinating and dehydrating agent for sensitive substrates to the aggressive and readily hydrolyzed acid chlorides such as PCl_5, $P(O)Cl_3$, thionyl chloride, and sulfonyl chloride. A great advantage can also be seen in the ability to the demands made by the various donor strengths of the substituents chosen for attachment to the phosphorus atom.[5] However, there are few reports about changing the halogen in the tetrahalomethane in the combination with tertiary phosphane system.[1a,6] Herein, we wish to report the halogen effects in Robinson–Gabriel type reaction of cyclopropanecarboxylic acid *N*′-substituted-hydrazides with PPh_3/CX_4 (X = Cl, Br, I) as dehydration agents.

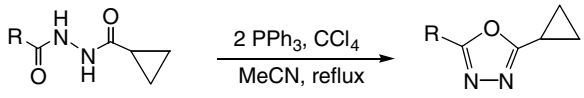
At first, we attempted the Robinson–Gabriel type reaction of disubstituted hydrazide **1a** with PPh_3/CCl_4 as a dehydration agent. We found that the reaction proceeded smoothly to give the desired oxadiazole product **2a** in 90% yield in acetonitrile under reflux with 2 equiv of PPh_3 and 1 equiv of CCl_4. The above reaction was found to be quite general. Other disubstituted hydrazides **1** bearing a variety of substituted phenyl groups (Table 1, entries 1–3), or a benzyl group (Table 1, entry 4), naphthalen-2-yl group (Table 1, entry 5), and a long aliphatic alkyl group (Table 1, entry 6) also underwent the dehydration and cyclization to give the corresponding oxadiazole products **2** in excellent yields under the similar reaction conditions within 2–10 h.

Interestingly, we found that when the reaction solution was refluxed for 2 days, trace amount of ring-opening product **3a** was obtained along with the product **2a** (Table 2, entry 1). Next, we utilized CBr_4 to replace CCl_4 for this reaction, the corresponding ring-opening product **4a** was formed in 16% yield along with the formation of the product **2a** in 79% yield after refluxing for

Keywords: Halogen effects; Robinson–Gabriel reaction; Cyclopropane; Ring-opening reaction; 2-(3-Halopropyl)-5-substituted-[1,3,4]-oxadiazole; Dehydration.
* Corresponding author. Fax: +86 21 64166128; e-mail: mshi@pub.sioc.ac.cn

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.048

Table 1. Reaction of cyclopropanecarboxylic acid *N*′-substituted-hydrazides **1** with PPh_3/CCl_4



1 **2**

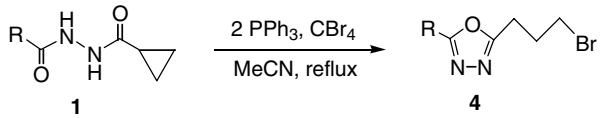
Entry	R	Time/h	Yield/[%][a] **2**
1	**1a**, *m*,*m*-$Me_2C_6H_3$	2	**2a**, 90
2	**1b**, C_6H_5	3	**2b**, 97
3	**1c**, *p*-$BuOC_6H_4$	3	**2c**, 99
4	**1d**, benzyl	10	**2d**, 80
5	**1e**, naphthalen-2-yl	10	**2e**, 96
6	**1f**, tridecyl	10	**2f**, 90

[a] Isolated yields.

2 h in acetonitrile (Table 2, entry 2). When the reaction solution was refluxed for 2 days, the product **4a** was formed in 91% yield as a sole product (Table 2, entry 3).

Under these optimized reaction conditions, the ring opening of other substrates was also investigated in the presence of PPh_3/CBr_4. The results are summarized in Table 3. A series of 2-(3-bromopropyl)-5-substituted-[1,3,4]oxadiazoles **4** were obtained in good yields for a variety of substrates **1**. The structure of **4a** was further determined by X-ray diffraction. The ORTEP drawing is shown in Figure 1.[7]

Table 3. Reaction of cyclopropanecarboxylic acid *N*′-substituted-hydrazides **1** with PPh_3/CBr_4

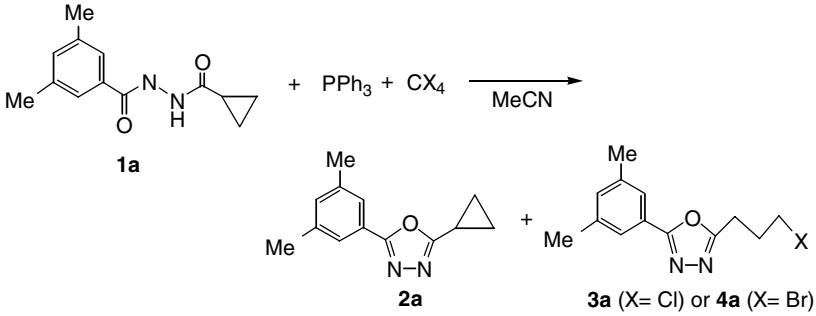


1 **4**

Entry	R	Time/d	Yield/[%][a] **4**
1	**1a**, *m*,*m*-$Me_2C_6H_3$	3	**4a**, 91
2	**1b**, C_6H_5	2	**4b**, 68
3	**1c**, *p*-$BuOC_6H_4$	2	**4c**, 90
4	**1d**, benzyl	2	**4d**, 67
5	**1e**, naphthalen-2-yl	3	**4e**, 96
6	**1f**, tridecyl	3	**4f**, 80

[a] Isolated yields.

Table 2. Difference in the reaction of **1a** with PPh_3/CCl_4 and PPh_3/CBr_4



Entry	CX_4	Temp./[°C]	Time	Yield/[%][a]	
				2a	**3a** or **4a**
1	CCl_4	Reflux	2 d	95	Trace
2	CBr_4	60	2 h	79	16
3	CBr_4	Reflux	2 d	0	91

[a] Isolated yields.

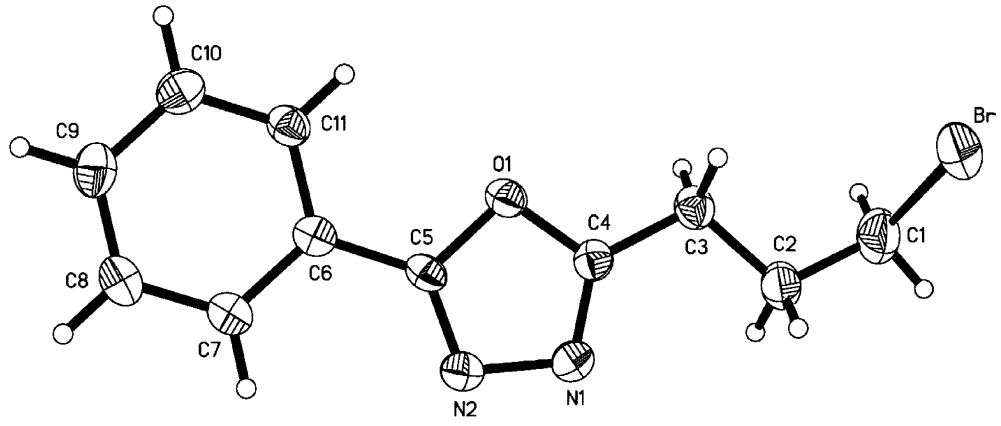
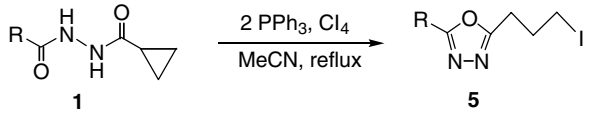


Figure 1. ORTEP drawing of **4a**.

Table 4. Reaction of cyclopropanecarboxylic acid *N*′-substituted-hydrazides **1** with PPh_3/Cl_4



1 **5**

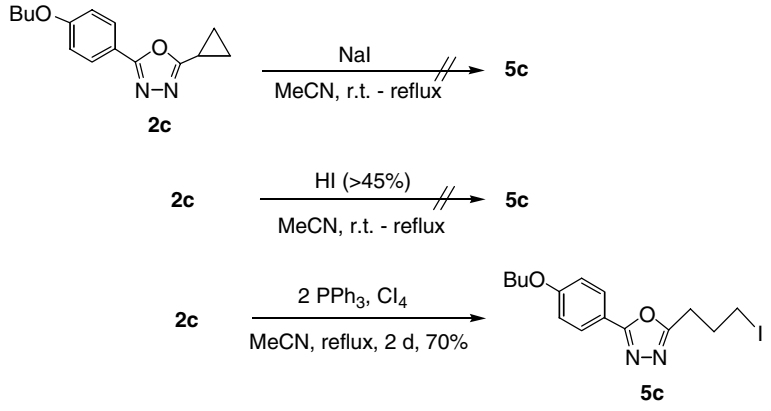
Entry	R	Time/d	Yield/[%][a] **5**
1	**1a**, *m*,*m*-$Me_2C_6H_3$	2	**5a**, 79
2	**1b**, C_6H_5	1	**5b**, 80
3	**1c**, *p*-$BuOC_6H_4$	2	**5c**, 75
4	**1d**, benzyl	1	**5d**, 54
5	**1e**, naphthalen-2-yl	1	**5e**, 66
6	**1f**, tridecyl	1	**5f**, 61

[a] Isolated yields.

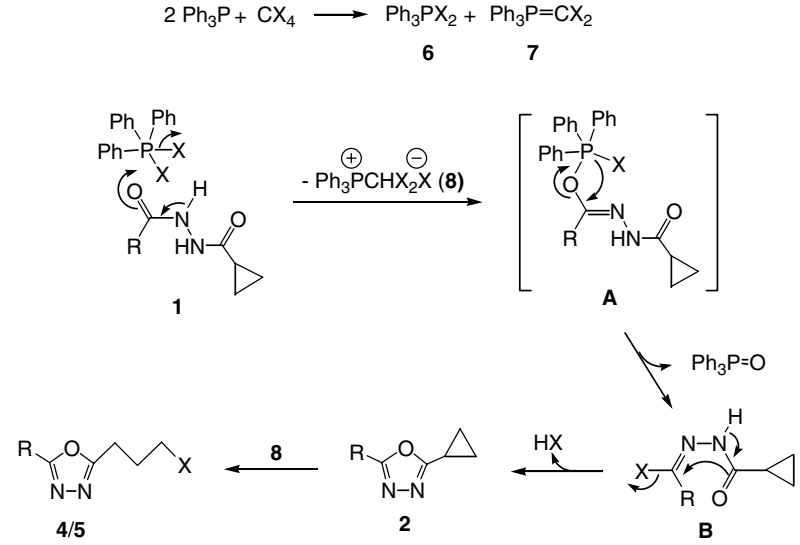
The ring-opening reaction was also investigated with CI_4 instead of CBr_4 under the similar conditions. As expected, the corresponding ring-opened products, 2-(3-iodopropyl)-5-substituted-[1,3,4]oxadiazoles, **5**, were cleanly afforded as sole products for a variety of substrates **1** (Table 4).

Formally, the ring-opened products **4** and **5** were the adducts of HX with the corresponding 2-cyclopropyl-5-substituted-[1,3,4]oxadiazoles **2**. However, 1,3,4-oxadiazole containing cyclopropyl group **2c** remained intact even after reflux for several days with NaI as a nucleophile (Scheme 1). On the other hand, aqueous solution of HI (>45%) caused the decomposition of compound **2c** and did not give the ring-opening product (Scheme 1). This result is similar to the sluggish reaction of other monoactivated cyclopropane system to a simple nucleophile.[8] At the present stage, we only found that the reagent of PPh_3/CBr_4 or PPh_3/CI_4 can promote this ring-opening reaction smoothly in MeCN to give the corresponding ring-opened product in good yield (Scheme 1).

Based on the above results and description in the literature about Robinson–Gabriel reaction,[9] a plausible reaction mechanism is proposed in Scheme 2. At first, triphenylphosphane reacts with carbon tetrahalide to give the corresponding dihalogentriphenylphosphorane **6** and dihalogenmethylene ylid **7**. Next, the intermediate **A** is formed by the reaction of cyclopropanecarboxylic



Scheme 1.



Scheme 2. A plausible reaction mechanism of bishydrazides **1** with PPh_3/CX_4.

acid N'-substituted-hydrazides **1** with dihalogentriphenylphosphorane **6** to release a dihalogenmethyltriphenylphosphonium salt **8** as white precipitates, which is dissolved in MeCN after the solution is heated to reflux.[4f,g] Thus, the corresponding *N*-substituted formimidoyl halogen **B** is formed along with the generation of triphenylphosphine oxide. After release of another HX, the corresponding 1,3,4-oxadiazole product **2** is given. The dihalogenmethyltriphenylphosphonium salt **8**, as a potential donor of HX, makes the subsequent ring-opening reaction take place and give the corresponding halogen displacement product **4** or **5**. As for Cl^-, because of its weak nucleophilicity, the ring-opening reaction is difficult to occur and the corresponding 1,3,4-oxadiazole product **2** with a cyclopropyl group is obtained.

In conclusion, we succeeded in preparing 1,3,4-oxadiazoles containing cyclopropyl group with most conveniently handled PPh_3/CCl_4 system. In the reaction, halogen effects were also observed and the corresponding 2-(3-halopropyl)-5-substituted-[1,3,4]oxadiazole products were obtained in good yields when CBr_4 or CI_4 was used instead of CCl_4. Efforts are underway to elucidate the mechanistic details and to extend the scope of this reaction.

Acknowledgments

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (20472096, 203900502, and 20272069).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.048.

References and notes

1. (a) Peesapati, V.; Chitty, S. V. *Indian J. Chem. Sect. B* **2003**, *42*, 616–620; (b) Sengupta, A. K.; Bajaj, O. P. *J. Ind. Chem. Soc.* **1978**, *55*, 108–110; (c) Fanshawe, W. J.; Bauer, V. J.; Safir, S. R.; Blickens, D. A.; Riggi, S. J. *J. Med. Chem.* **1969**, *12*, 381–383; (d) Al-Talib, M.; Tashtoush, H.; Odeh, N. *Synth. Commun.* **1990**, *20*, 1811–1817; (e) Hutt, M. P.; Elslager, E. F.; Werbel, L. M. *J. Heterocycl. Chem.* **1970**, *7*, 511–518; (f) Havranek, R. E.; Hoey, G. B.; Baeder, D. H. *J. Med. Chem.* **1966**, *9*, 326–328; (g) Ainsworth, C.; Buting, W. E.; Davenport, J.; Callender, M. E.; MeCowen, M. C. *J. Med. Chem.* **1967**, *10*, 208–211; (h) Qin, Y.; Wang, M.; Gao, Z. *Youji huaxue* **1986**, 422–428.
2. (a) Kovacs, H.; Delman, A. P.; Simms, B. B. *J. Polym. Sci. Part A-1* **1970**, *8*, 869–884; (b) Hyman, M. J. U.S. Patent 4017738, 1977; *Chem. Abstr.* **1977**, *87*, 30194; (c) Suman, S. P.; Bahel, S. C. *Agric. Biol. Chem.* **1979**, *43*, 1339–1341; (d) Valenti, S. Br. Patent 1550440, 1979; *Chem. Abstr.* **1980**, *92*, 199758.
3. (a) Balsells, J.; DiMichele, L.; Liu, J.; Kubryk, M.; Hansen, K.; Armstrong, J. D. *Org. Lett.* **2005**, *7*, 1039–1042; (b) Perez, M. A.; Bermejo, J. M. *J. Org. Chem.* **1993**, *58*, 2628–2630; (c) Tashtoush, H.; Al-Talib, M.; Odeh, N. *Ann. Chem.* **1992**, 291; (d) Shi, W.; Qian, X.; Song, G.; Zhang, R.; Li, R. *J. Fluroine Chem.* **2003**, *106*, 173–179; (e) Mogilaigh, K.; Chowdary, D. S.; Rao, R. B. *Indian J. Chem. Sect. B* **2001**, *40*, 43–48.
4. (a) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811; (b) Rabinowitz, R.; Marcus, R. *J. Am. Chem. Soc.* **1962**, *84*, 1312–1313; (c) Ramirez, F.; Desai, N. B.; Mckelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1145–1347; (d) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; Wiley Interscience: New York, 1972; Vol. 3, p 320; (e) Gadogan, J. I. G.; Mackie, R. K. *Chem. Soc. Rev.* **1974**, *3*, 87–137; (f) Tömösközi, I.; Gruber, L.; Radics, L. *Tetrahedron Lett.* **1975**, *16*, 2473–2476; (g) Aneja, R.; Davies, A. P.; Knaggs, J. A. *Tetrahedron Lett.* **1974**, *15*, 67–70.
5. (a) Friederang, A. W.; Tarbell, D. S. *J. Org. Chem.* **1968**, *33*, 3797–3800; (b) Castrol, B.; Chapleur, Y.; Gross, B.; Selve, C. *Tetrahedron Lett.* **1972**, *11*, 5001–5004; (c) Downie, I. M.; Lee, J. B.; Matough, M. F. S. *J. Chem. Soc., Chem. Commun.* **1968**, 1350–1351; (d) Boigegrain, R.; Castrol, B.; Selve, C. *Tetrahedron Lett.* **1975**, *16*, 2529–2530; (e) Appel, R.; Warning, K.; Ziehn, K.-D. *Justus Liebigs Ann. Chem.* **1975**, 406–409.
6. Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32–35.
7. The crystal data of **4a** has been deposited in CCDC with number 264863. Empirical Formula: $C_{11}H_{11}N_2OBr$; Formula Weight: 267.13; Crystal size: $0.512 \times 0.487 \times 0.169$; Crystal Color: Habit: colorless, prismatic; Crystal System: Monoclinic; Lattice Type: Primitive; Lattice Parameters: $a = 13.511(2)$ Å, $b = 10.6087(18)$ Å, $c = 8.0276(14)$ Å, $\alpha = 90°$, $\beta = 104.186(4)°$, $\gamma = 90°$, $V = 1115.6(3)$ Å^3; Space group: $P2(1)/c$; $Z = 4$; $D_{calc} = 1.590$ g/cm^3; $F_{000} = 536$; $R1 = 0.0718$, $wR2 = 0.1824$. Diffractometer: Rigaku AFC7R.
8. (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72; (b) Avilov, D. V.; Malusare, M. G.; Arslancan, E.; Dittmer, D. C. *Org. Lett.* **2004**, *6*, 2225–2228; (c) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2003**, *5*, 4281–4284; (d) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987–995; (e) Truce, W. E.; Lindy, L. B. *J. Org. Chem.* **1961**, *27*, 1463–1467; (f) Smith, A. B.; Scarborough, R. M. *Tetrahedron Lett.* **1978**, *19*, 1649–1652; (g) Ogoshi, H.; Setsune, J.-I.; Yoshida, Z.-I. *J. Organomet. Chem.* **1980**, *185*, 95–104; (h) Ogoshi, H.; Kikuchi, Y.; Yamaguchi, T.; Toi, H.; Aoyama, Y. *Organometallics* **1987**, *6*, 2175–2178; (i) Hwu, J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 452–453; (j) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147–3150; (k) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 4333–4336.
9. Wasserman, H. H.; Vinick, F. J. *J. Org. Chem.* **1973**, *38*, 2407–2408.