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Synthesis of Geminal Azido−Halo Compounds and α-Azidoalkyl Esters from Aldehydes via α-Azido Alcohols

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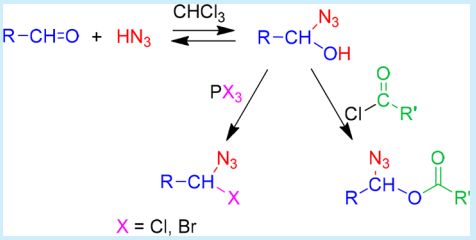
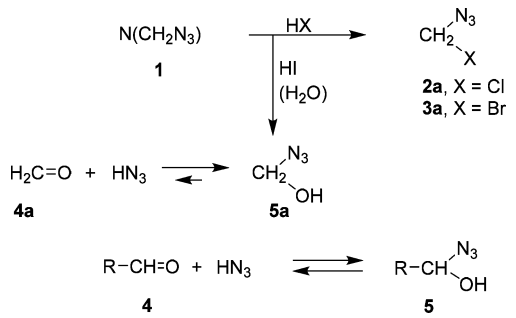
Supporting Information

ABSTRACT: α-Azido alcohols are generated by treating aldehydes with hydrazoic acid in chloroform. These adducts are transformed into geminal azido−halo compounds through the reaction with phosphorus trichloride or phosphorus tribromide, whereas α-azidoalkyl esters are isolated after interaction with acyl chlorides.



Alcohols and the azido unit belong to the most important functional groups in organic chemistry. Especially unusual structures and new reactions of azides have currently elicited great research interest.[1,2] However, α-azido alcohols of type **5**, the geminal combination of both functionalities, are only recently known (Scheme 1).[3] Such compounds were accidentally discovered after preparing azidochloromethane **2a** and azidobromomethane **3a** by treatment of triazide **1** with anhydrous hydrogen chloride or hydrogen bromide, respectively.[4] These products are not available by the simple reaction of dihalomethanes with azide salts because the desired nucleophilic substitution is by far slower than the displacement of the second halogen atom leading to unwanted diazidomethane.[5] When chloroiodomethane was treated with a substoichiometric amount of hexadecyltributylphosphonium azide (QN_3),[6] we hoped to detect intermediate **2a** by NMR monitoring, but were disappointed since only the signals of the substrate, diazidomethane, and those of Q (hexadecyltributylphosphonium) were observed.[4]

Scheme 1. Discovery of Azidomethanol 5a and Synthesis of α-Azido Alcohols 5



In an attempt to prepare azidoiodomethane by treatment of **1** with hydrogen iodide under apparently not completely anhydrous conditions or workup, we surprisingly obtained azidomethanol **5a** instead of the desired product.[3] The new compound **5a** was conveniently characterized[3] in solution although it was only postulated to occur as a short-lived intermediate previously.[7] Approximately three decades ago, several unsuccessful experiments[8] to synthesize α-azido alcohols **5** led to the presumption that hydrazoic acid does not react with aldehydes readily.[9] But **5a** was simply available by mixing solutions of formaldehyde **4a** and hydrazoic acid, and it turned out that all types of aldehydes **4** react with the reagent HN_3 to establish an equilibrium with **5**.[3] At −50 to −65 °C, this equilibration is retarded, and thus, hydrazoic acid along with the solvent and even volatile aldehydes **4** can be removed in vacuum to get highly enriched or pure α-azido alcohols **5**, which are obtained as less volatile solids or viscous liquids.[3,10] When the adduct **5** is liberated from HN_3 at room temperature, however, the rapid equilibration causes complete cleavage of **5**, and only aldehyde **4** remains. In such cases, the formation of **5** from **4** and hydrazoic acid is easily overlooked,[11] and this explains the late discovery of α-azido alcohols.[3]

The synthesis of adducts **5** from aldehydes and HN_3 is compatible with a variety of other functional groups, such as olefins, alkynes, allenes, halides, acetals, esters, et al., and can be combined with several subsequent transformations. Thus, 1,3-dipolar cycloaddition at the azido group of **5** led to 1,2,3-triazoles, for example, by copper-free click reaction in the presence of cyclooctyne. Photolysis of **5** induced liberation of dinitrogen and gave amides via a proton shift from carbon to nitrogen or similar migration of the group R.[3,10,12] Furthermore, the azido unit in **5** strongly influences the facility with which the hydroxy group can be oxidized to a carbonyl group. Hence, oxidation of α-azido alcohols **5** in chloroform at −20 to −60 °C with the help of pyridinium chlorochromate produced the corresponding acyl azides in 80−89% yield based on the aldehydes **4**.[3] Under such mild reaction conditions,

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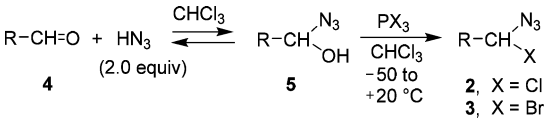
Org. Lett. XXXX, XXX, XXX−XXX

Curtius rearrangement did not occur, and even previously unknown short-lived formyl azide was available from azidomethanol **5a** for the first time.[13] Moreover, cleavage of 1,2-diazidoethan-1,2-diol, which is accessible from glyoxal and hydrazoic acid, gave formyl azide by treatment with periodic acid.

However, the equilibration of **4**/HN_3 and **5** has to be taken into account when transformations of **5** are planned. In the presence of a base, for example, hydrazoic acid is completely consumed to form a salt, and the equilibrium is totally shifted from **5** to **4**. Herein, we describe esterification of **5** with the help of acyl chlorides and the synthesis of geminal azido–halo compounds **2** and **3** from **5** and phosphorus trihalide (Table 1).

Table 1. Synthesis of Geminal Azido–Halo Compounds 2 and 3 from Aldehydes 4 via α-Azido Alcohols 5



compd	R	yield of **2** (%)[a]	yield of **3** (%)[a]
a	H	56[b]	67[b]
b	Me	66[b]	–[c]
c	Et	65[b]	–[c]
d	CH_2Cl	42	48
e	CCl_3	42	50
f	CO_2Et	49	54
g	Bn	90[b]	–[c]

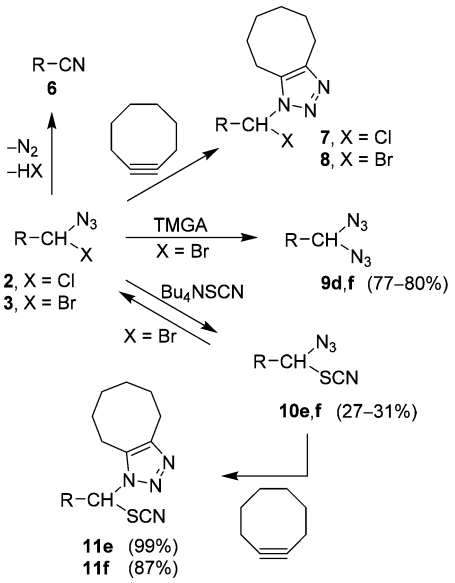
[a]Isolated yields based on **4** unless stated otherwise. [b]Yield determined by ^1H NMR and based on **4**. [c]Unstable product, decomposition leading to nitrile **6**.

Very few examples of products, for which structures **2**[14] or **3**[15] were assigned, are known in literature.[16] But to the best of our knowledge, a general method to prepare such compounds has not been reported so far. Obviously, the access to **2a** and **3a** from the special precursor **1** cannot be transfused from these parent compounds to create a general synthesis of geminal azido–halo products. On the other hand, several compounds of type **2** were analyzed in theoretical studies.[17]

When we treated freshly distilled aldehydes **4** with 2 equiv of hydrazoic acid[18,19] in chloroform,[20] first at −5 °C and then at room temperature for 2 h, the α-azido alcohols **5** were formed. These products were liberated from solvent and an excess of HN_3 in vacuum (0.005 mbar) at −50 to −55 °C, which led also to removal of unreacted **4** in the case of more volatile substrates. The residue was resolved in precooled (−50 °C) chloroform, and after addition of 3 equiv of phosphorus trihalide, the mixture was stirred for 1 h and then at ambient temperature for 12 h. The latter reaction conditions were changed to −30 °C and 12 h for the less stable products **2b,c,g**. The procedure of workup was also dependent on the stability and volatility of the products **2** and **3**. Isolation of these substances after conventional workup with water and pentane/diethyl ether was possible for **2d–f** and **3d–f** and gave moderate yields (Table 1). In the case of less robust and/or highly volatile products, we avoided aqueous workup and complete removal of the solvent because of the decay or evaporation loss of the substances. The unwanted decomposition of geminal azido–halo compounds **2** and **3** to generate nitriles **6** was excessive for bromides **3b,c,g**, which could not be detected even by NMR spectroscopy. The explosive properties of the products, especially those of azides with low molecular mass, must also be taken into account.[19] Thus, we treated not only most of the azides **2** and **3** but also the compounds **9**, **10**, **13**, **14**, **17**, **19e**, and **20e** with cyclooctyne in dichloromethane or hexane and obtained the corresponding 1*H*-1,2,3-triazoles in good to excellent yields. These cycloadducts, for example, **7**, **8**, and **11**, are stable and can easily be utilized to characterize the original azides.

The products **2** and **3** show the quality of substrates with a halide leaving group combined with an adjacent azido donor unit. Consequently, high reactivity, comparable to that of α-halo ethers, is observed. This reactivity can be used in substitution and elimination reactions as depicted in Schemes 2 and 3, respectively. Treatment of **3d** or **3f** with *N*,*N*,*N*′,*N*′-

Scheme 2. Reactions of Geminal Azido–Halo Compounds 2 and 3



tetramethylguanidinium azide (TMGA) in chloroform led to the corresponding geminal diazides **9d** and **9f**, which are known[16,21] compounds. Obviously, the reactivity of the geminal azido–halo moiety is significantly higher than that of the CH_2–Cl group of **3d** in this substitution reaction. Exposure of **3e** or **3f** to an excess of tetrabutylammonium thiocyanate in chloroform gave only incomplete consumption of the starting compounds and low yields of **10e** and **10f**, respectively. Even after extended reaction times, 30–31% of **3e** or **3f** were recovered. Most probably, the substrates form equilibria with the desired products.[22]

The vinyl azides **12–14** and **17** were generated when we reacted geminal azido–halo compound **2g**, **2d**, or **3d** with potassium *tert*-butoxide in diethyl ether. The known[23] product **12** was isolated in 74% yield as a *cis*/*trans* mixture (1:9). In the cases of enazides **13**, **14**, and **17**, characterization was performed only partially and in solution because of the explosive and volatile properties of these products. After treatment with cyclooctyne, however, the corresponding cycloadducts **15**, **16**, and **18** were utilized to isolate stable derivatives, which were conveniently characterized.[24]

Esterification of α-azido alcohols **5** is possible with the help of acyl chlorides and leads to isolable products **19** and **20** (Table 2). After removal of hydrazoic acid and aldehyde **4** in

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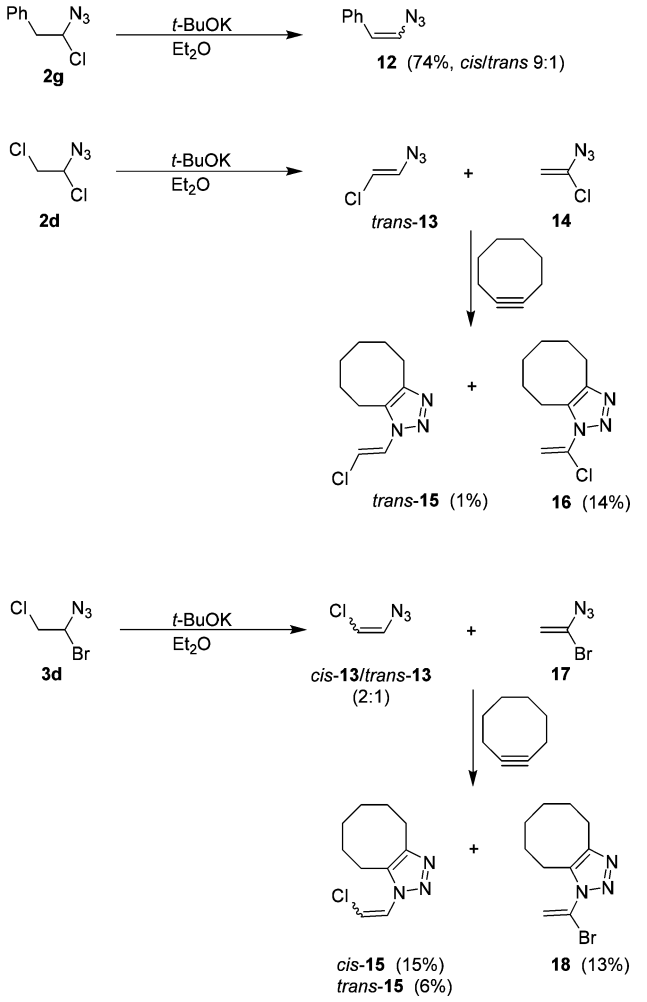
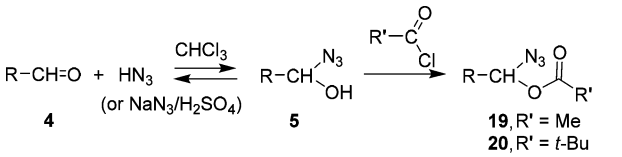
Scheme 3. Synthesis of Vinyl Azides from Geminal Azido–Halo Compounds[a]



[a]Isolated yields based on **2d**, **2g**, and **3d**.

vacuum, we first treated solutions of highly enriched adducts **5** with acetyl chloride or pivaloyl chloride (Method A). However, it turned out that this purification of **5** was not necessary, and even significantly better yields of **19** were achieved in some cases by using the equilibration mixture of **4**/HN_3 and **5** for the reaction with the acyl chloride (Method B). A one-pot procedure, starting with aldehyde **4** in chloroform at −35 °C and successive addition of acyl chloride, concentrated sulfuric acid, and sodium azide, was also successful to prepare **19** and **20** via intermediate formation of **5** (Method C). In this procedure, additional handling of solutions of explosive and toxic hydrazoic acid[18,19,25] was not necessary, and a substoichiometric amount of sulfuric acid was adequate to produce the reagent from sodium azide because hydrogen chloride as a second strong acid is generated in the esterification step. From simple aldehydes such as **4b** and **4c** acetates **19** (R′ = Me) were synthesized with moderate yields via α-azido alcohols **5b,c**, whereas good to excellent yields of acetates resulted from electron-poor substrates such as **4e** and **4f**. However, the sterically hindered pivaloyl chloride gave only low yields of the corresponding esters **20b,e,f** (R′ = *t*-Bu). In all cases, α-azidoalkyl esters **19** and **20** were isolated as colorless liquids, and the products **19e** and **20e** were additionally treated

Table 2. Synthesis of α-Azidoalkyl Esters 19 and 20 from Aldehydes 4 via α-Azido Alcohols 5



compd **4**	R	method[a]	yield of **19** (%)[b]	yield of **20** (%)[b]
b	Me	A	34	–
b	Me	B	44	–
b	Me	C	34	10
c	Et	A	23	–
c	Et	B	23	–
c	Et	C	54	–
e	CCl_3	A	70	12
e	CCl_3	B	100	12
e	CCl_3	C	–	15
f	CO_2Et	A	79	13
f	CO_2Et	B	100	15

[a]Method A included enrichment of **5** by removal of HN_3 and **4**; the equilibration mixture of **4**/HN_3 and **5** was utilized in Method B; in the case of Method C, a one-pot procedure with **4**, acyl chloride, H_2SO_4, and NaN_3 was used. [b]Isolated yields based on **4**.

with cyclooctyne to prepare the corresponding 1*H*-1,2,3-triazoles.[24]

The syntheses of α-azidoalkyl esters by alternative methods is known in literature.[26] But the access to these compounds is often described for single and special examples only, and the desired products are formed as mixtures with other substances in many cases.[27] To date, simple aldehydes have not been utilized to prepare α-azidoalkyl esters.

In summary, we have shown that geminal azido–halo compounds **2** and **3** as well as α-azidoalkyl esters **19** and **20** can easily be prepared from aldehydes **4** via α-azido alcohols **5**. We assume that the adducts **5** can also be used to synthesize other products with rare combinations of geminal functional groups. Thus, we hope α-azido alcohols **5** will further enrich the multifarious chemistry of organic azides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02380.

Experimental details for new reactions and analytical data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Firdous (Chemnitz University of Technology) for some experiments with compound **3f**.

REFERENCES

(1) For recent reviews about organic azides, see: (a) Bräse, S., Banert, K., Eds. *Organic Azides: Syntheses and Applications*; Wiley: Chichester, 2010. (b) Häring, A. P.; Kirsch, S. F. *Molecules* **2015**, *20*, 20042−20062. (c) Huang, X.; Groves, J. T. *ACS Catal.* **2016**, *6*, 751−759. (d) Hu, B.; DiMagno, S. G. *Org. Biomol. Chem.* **2015**, *13*, 3844−3855. (e) Zhang, X.; Zhang, Y. *Molecules* **2013**, *18*, 7145−7159. (f) Tanimoto, H.; Kakiuchi, K. *Nat. Prod. Commun.* **2013**, *8*, 1021−1034. (g) Chapyshev, S. V. *Molecules* **2015**, *20*, 19142−19171.

(2) For selected recent examples, see: (a) Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356−5359. (b) Song, W.; Kozhushkov, S. I.; Ackermann, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6576−6578. (c) Banert, K.; Arnold, R.; Hagedorn, M.; Thoss, P.; Auer, A. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 7515−7518. (d) Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600−604. (e) Yuan, Y.-A.; Lu, D.-F.; Chen, Y.-R.; Xu, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 534−538. (f) Banert, K.; Richter, S.; Schaarschmidt, D.; Lang, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3499−3502. (g) Lu, M.-Z.; Wang, C.-Q.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 6110−6113. (h) Nocquet-Thibault, S.; Rayar, A.; Retailleau, P.; Cariou, K.; Dodd, R. H. *Chem. - Eur. J.* **2015**, *21*, 14205−14210. (i) Banert, K.; Hagedorn, M.; Wu, Z.; Zeng, X. *Molecules* **2015**, *20*, 21328−21335. (j) Klahn, P.; Erhardt, H.; Kotthaus, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 7913−7917.

(3) Banert, K.; Berndt, C.; Firdous, S.; Hagedorn, M.; Joo, Y.-H.; Rüffer, T.; Lang, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 10206−10209.

(4) Banert, K.; Joo, Y.-H.; Rüffer, T.; Walfort, B.; Lang, H. *Tetrahedron Lett.* **2010**, *51*, 2880−2882.

(5) Hassner, A.; Stern, M.; Gottlieb, H. E.; Frolow, F. *J. Org. Chem.* **1990**, *55*, 2304−2306.

(6) Banert, K. *Synthesis* **2007**, 3431−3446.

(7) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171−3174.

(8) See, for example: Birkofer, L.; Kaiser, W. *Justus Liebigs Ann. Chem.* **1975**, 266−274.

(9) Hassner, A.; Fibiger, R.; Amarasekara, A. S. *J. Org. Chem.* **1988**, *53*, 22−27.

(10) Banert, K. *Synthesis* **2016**, *48*, 2361−2375.

(11) Some examples of treating aldehydes with HN_3, in which generation of **5** was overlooked: (a) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5248−5252. (b) Davies, A. J.; Donald, A. S. R.; Marks, R. E. *J. Chem. Soc. C* **1967**, 2109−2112. (c) Szmuszkovicz, J.; Kane, M. P.; Laurian, L. G.; Chidester, C. G.; Scahill, T. A. *J. Org. Chem.* **1981**, *46*, 3562−3564. (d) Gauthier, C.; Ramondenc, Y.; Plé, G. *Tetrahedron* **2001**, *57*, 7513−7517. (e) Kim, S.-G.; Park, T.-H. *Synth. Commun.* **2007**, *37*, 1027−1035.

(12) Cheng, J.; Gu, Z.; He, C.; Jin, J.; Wang, L.; Li, G.; Sun, B.; Wang, H.; Bai, J. *Carbohydr. Res.* **2015**, *414*, 72−77.

(13) Banert, K.; Berndt, C.; Hagedorn, M.; Liu, H.; Anacker, T.; Friedrich, J.; Rauhut, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4718−4721.

(14) Chatterjee, B. G.; Venkateswara Rao, V.; Moza, P. N. *Tetrahedron* **1967**, *23*, 499−503.

(15) Mitachi, K.; Salinas, Y. G.; Connelly, M.; Jensen, N.; Ling, T.; Rivas, F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4536−4539.

(16) For a synthesis of 2-azido-2-haloacetates, see: Takeuchi, Y.; Takagi, K.; Yamaba, T.; Nabetani, M.; Koizumi, T. *J. Fluorine Chem.* **1994**, *68*, 149−154.

(17) (a) Lee, I.; Chung, D. S.; Jung, H. J. *Tetrahedron* **1994**, *50*, 7981−7986. (b) Glidewell, C.; Holden, H. D. *J. Mol. Struct.: THEOCHEM* **1982**, *89*, 325−332.

(18) Although we never encountered any problems when handling solutions of hydrazoic acid, we point out that this reagent is not only very explosive but also highly volatile and toxic. Thus, solutions of hydrazoic acid should be handled in a hood. In any case, isolation of the undiluted compound, for example, after removal from a high-boiling solvent, has to be avoided.

(19) ***Caution!*** For the potential hazardous properties of hydrazoic acid and organic azides, see: Keicher, T.; Löbbecke, S. In *Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K., Eds; Wiley: Chichester, 2010; pp 3−27.

(20) The equilibrium of **4**/HN_3 and **5** was also investigated in other solvents. Details are explained in the Supporting Information, p S-2.

(21) Weigand, K.; Singh, N.; Hagedorn, M.; Banert, K. *Org. Chem. Front.* **2017**, *4*, 191−195.

(22) For other examples of such equilibria, see: Ohtani, N.; Murakawa, S.; Watanabe, K.; Tsuchimoto, D.; Sato, D. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1851−1856.

(23) (a) Chakraborty, T. K.; Reddy, G. V. *Tetrahedron Lett.* **1990**, *31*, 1335−1338. (b) Nair, V.; George, T. G. *Tetrahedron Lett.* **2000**, *41*, 3199−3201. (c) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888−889.

(24) For details, see the Supporting Information.

(25) Banert, K. In *Electronic Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 2013; pp 3−8.

(26) McGirk, R. H.; Cyr, C. R.; Ellis, W. D.; White, E. H. *J. Org. Chem.* **1974**, *39*, 3851−3855.

(27) (a) Loren, J. C.; Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Synlett* **2005**, 2847−2850. (b) Riehl, J.-J.; Casara, P.; Fougerousse, A. *C. R. Acad. Sci., Ser. C* **1974**, *279*, 113−115. (c) Keschmann, E.; Zbiral, E. *Liebigs Ann. Chem.* **1973**, 1445−1456. (d) Wolloch, A.; Zbiral, E.; Haslinger, E. *Liebigs Ann. Chem.* **1975**, 2339−2354. (e) Kyba, E. P.; Alexander, D. C. *Tetrahedron Lett.* **1976**, *17*, 4563−4564. (f) Huang, W.-Y.; Lü, L. *Chin. J. Chem.* **1992**, *10*, 365−372.

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