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The one-pot synthesis of 4-aryl-1*H*-1,2,3-triazoles without azides and metal catalization

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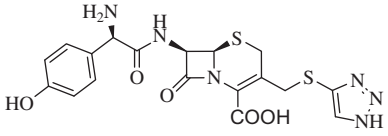
ABSTRACT

In this study, a new methodology for the one-pot synthesis of 4-aryl-1*H*-1,2,3-triazoles from aryl-glyoxaldoxime semicarbazone is presented. 4-Aryl-1,2,3-triazoles were obtained in moderate to good yields via sodium dithionite and O_2, which are all efficient, safe and inexpensive reagents. This reaction is more suitable for large-scale syntheses than those using hydrazoic acid, sodium azide, or organic azides.

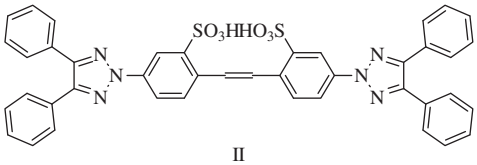
1,2,3-Triazole is a significant class of nitrogen heterocycles[1] which are widely used as pharmaceuticals and agrochemicals. 1,2,3-Triazole displays the broad spectrum of biological activities[2] such as antibacterial (I, Cefatrizine, Fig. 1), herbicidal, fungicidal, antiallergic, and anti-HIV properties. Compounds containing 1,2,3-triazoles have found industrial applications[3] such as dyes, corrosion inhibitors, and photostabilizers (II, Fig. 1). Moreover, 4-aryl-1*H*-1,2,3-triazoles have been employed as human methionine aminopeptidase (hMetAP2) and indoleamine 2,3-dioxygenase (IDO) inhibitors, and are expected to become medicines to treat cancers, AIDS, Alzheimer's disease, tristimania, cataracts, and some other serious diseases.[4] For instance, Rufinamide[5] (III, Fig. 1) is a new CNS-active compound used in the treatment of epilepsy, which is approved by the FDA and listed in the United States on November 2008.

Because of the importance of this structural motif, there are a variety of practical methods available for the preparation of 1,2,3-triazole. Among them, the Huisgen azide–alkyne dipolar cycloaddition[6] (AAC) is perhaps the most universally utilized method for the synthesis.

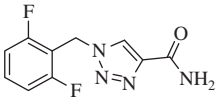
In order to solve the drawbacks[7] such as lack of regioselectivity when utilizing unsymmetrical alkynes and a long reaction time, the Huisgen dipolar cycloaddition of alkynes to organicazides had been greatly developed in the following three aspects:



I



II



III

Figure 1. Structure of some bioactive compounds.

(1) The AAC reaction takes place with the same dipolarophile (mainly is terminal alkyne), but different 1,3-dipoles, for example exploiting TSE-N_3[7] (β-Tosylethylazide), TMS-N_3[8a] (trimethylsilylazide), MeOPEG-N_3[8b] (poly(ethyleneglycol)-

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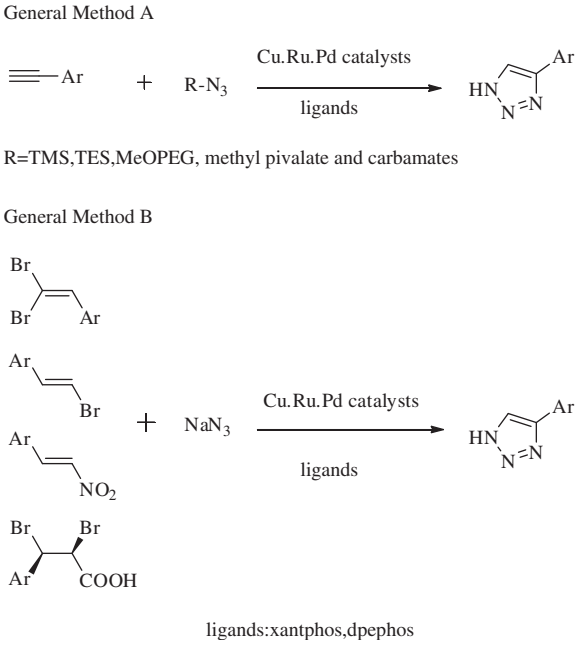


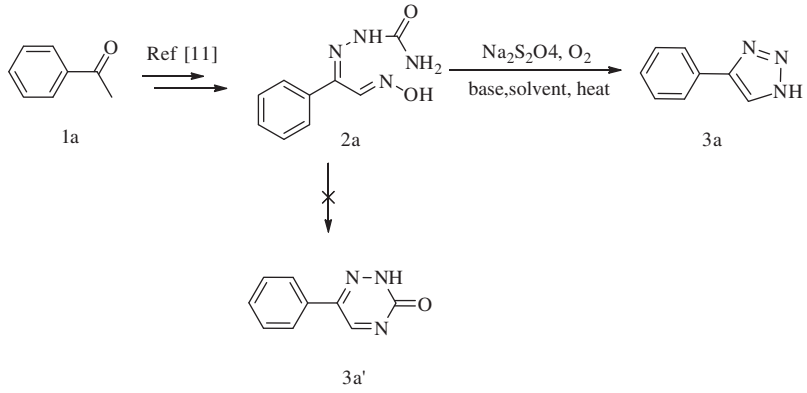
Scheme 1.

supportedazide), azidomethyl pivalate, azidomethyl morpholine-4-carboxylate, and azidomethyl *N*,*N*-diethylcarbamate[8c] to replace sodium azide and hydrazoic acid in order to avoid jeopardizing the safety of large-scale syntheses (Scheme 1, General Method A).

(2) The AAC reaction takes place with the same 1,3-dipole (commonly is sodium azide), but different dipolarophiles, such as using β-bromostyrene,[9a] 1,1-dibromoalkenes,[9b] anti-3-aryl-2, 3-dibromopropanoic acids,[9c] and nitrostyrene[9d] which were more easily obtained than terminal alkyne (Scheme 1, General Method B).

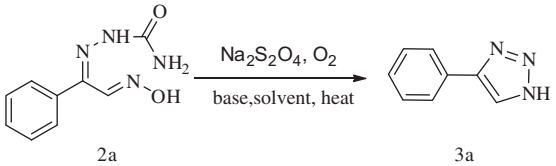
(3) The AAC takes place with different catalysts and different ligands (including Pd-, Ru-, Cu-catalyzed (Cu^0, Cu^{1+}, Cu^{2+}) reaction and xantphos, dpephos)[8,9] which were applied in the foregoing methods to undergo the AAC reaction at room temperature and improve regioselectivity as well as shorten the reaction time.

Although great contribution have been made to the AAC reaction, there are still several problems that organic azides are synthesized from sodium azide[8] which is a highly toxic, explosive reagent,[8d] and metal catalysts, especially ligands[9] as mentioned above are expensive and not easy to prepare. So a general, simple, and scalable method for the synthesis of 4-aryl-1*H*-1,2,3-triazoles



Scheme 2.

Table 1
Screening of the reaction conditions[a]

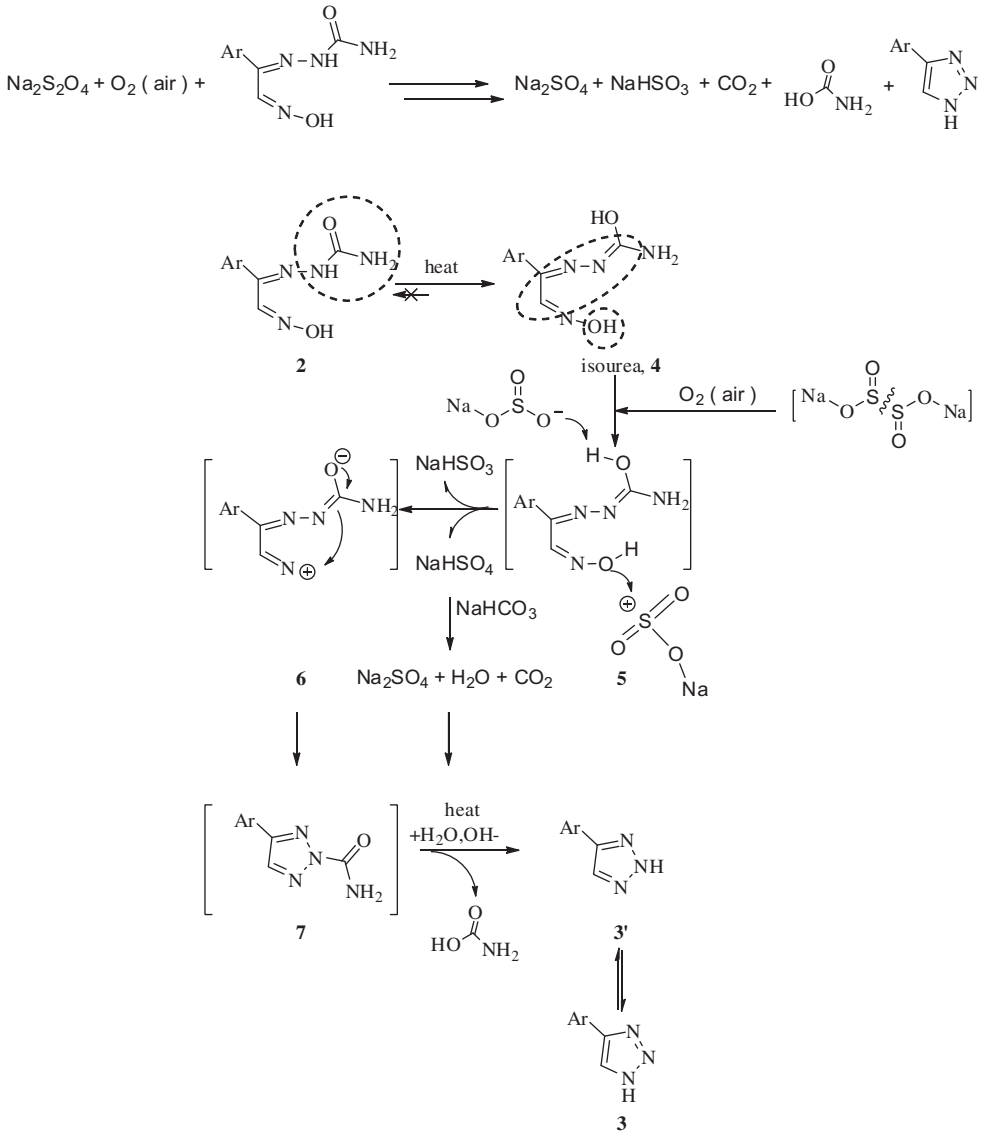


	Dehydrating agent	Oxidizing agent	Base	Solvent	Temperature (°C)	Time[b]	Yield[c] (%)
1	–	O_2 in air	$NaHCO_3$	DMF	110	>5 h	20
2	–	O_2 in air	NaOH	DMF	110	>5 h	22
3	–	O_2 in air	Na_2CO_3	DMF	110	>5 h	21
4	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	DMF	110	0.5 h	65
5	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	DMSO/H_2O	100	1 h	54
6	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	Toluene/H_2O	100	>5 h	NR
7	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	DMF/H_2O	100	30 min	85
8	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	DMF/-	100	1 h	70

Table 1 (*continued*)

	Dehydrating agent	Oxidizing agent	Base	Solvent	Temperature (°C)	Time[b]	Yield[c] (%)
9	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	DMF/H_2O[d]	90	5 h	42
10	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	DMF/H_2O	110	15 min	95
11	$Na_2S_2O_4$	O_2 in air	$NaHCO_3$	DMF/H_2O	120	15 min	96
12	$Na_2S_2O_4$	O_2 in air	—	DMF/H_2O	110	>5 h	NR
13	$Na_2S_2O_4$	O_2 in air	$KHCO_3$	DMF/H_2O	110	1.5 h	85
14	$Na_2S_2O_4$	O_2 in air	NaOH	DMF/H_2O	110	30 min	87
15	$Na_2S_2O_4$	O_2 in air	Na_2CO_3	DMF/H_2O	110	1 h	82
16	$Na_2S_2O_4$	-[e]	$NaHCO_3$	DMF	110	>5 h	NR
17	$Na_2S_2O_4$	Pure O_2[f]	$NaHCO_3$	DMF/-	110	25 min	80
18	$Na_2S_2O_4$	Pure O_2	$NaHCO_3$	DMF/H_2O	110	10 min	98

[a] Reactions were carried out with 0.25 mmol of **2a** (1 equiv), $Na_2S_2O_4$ (2 equiv), base (4 equiv), and solvent (5 mL).
[b] Complete reaction time of substrates.
[c] Isolated yield by column chromatography.
[d] DMF was the main solvent and the addition water was used to accelerate basic hydrolysis after the $Na_2S_2O_4$ was added after 5 min.
[e] The reactions was taken in the Schlenk tube to get rid of O_2.
[f] 1 Atm pure O_2.



Scheme 3.

is still not available. Herein, we report our findings for the one-pot synthesis of 4-aryl-1*H*-1,2,3-triazoles from arylglyoxaldoxime semicarbazone.

We observed the formation of 4-phenyl-1*H*-1,2,3-triazole (**3a**) (Scheme 2) in the process of synthetic study toward 6-phenyl-1,2,4-triazin-3(2*H*)-one (**3a**′). When sodium dithionite was chosen

as the deprotection agent of the aldoxime, it did not produce the desired products **3a′**, instead of a pure white solid characterized as **3a** by ^{1}H NMR, ^{13}C NMR, MS, and melting point.[10] With the unexpected and unpredictable result, our investigation began with an effort to optimize reaction conditions for the one-pot synthesis of 4-aryl-1*H*-1,2,3-triazoles.

For exploratory experiments, the unsubstituted aryl methyl ketones **1a** were used as a representative substrate. Firstly, the intermediate **2a** was prepared as per the literature procedures reported by Trust.[11] Then various bases, temperatures and solvents were used for screening the best condition of cycloaddition reactions. Progress of the reaction was monitored by TLC and the results are shown in Table 1.

At first, test experiments were carried out with different bases. It can be found that less product was obtained in low yield (Table 1, entries 1–3). The corresponding product could be obtained in a higher yield because of $Na_2S_2O_4$'s participation (Table 1, entry 4). Through an examination of the influence of solvents (Table 1, entries 5–8), DMF and water were the best solvents and superior over the other solvents in terms of both product yield and reaction time (Table 1, entry 7), where DMF was the main solvent and the addition of water was used to accelerate basic hydrolysis after the $Na_2S_2O_4$ was added after 5 min. Encouraged by this result, we then investigated the effect of the temperature on the model reaction. It was pleasing to find that the desired product **3a** was obtained in a yield of 95% when the reaction was performed at 110 °C for 15 min (Table 1, entry 10).

Then a series of four bases was screened to find the best base for the reaction (Table 1, entries 10 and 12–15). And the result showed that $NaHCO_3$ worked best. Finally, in order to confirm the role of oxygen, the reaction was carried out in the absence of O_2. It was found that O_2 was essential for the reaction (Table 1, entries 16–18). Thus, the optimized reaction condition for the one-pot synthesis was $Na_2S_2O_4$ (2 equiv), $NaHCO_3$ (4 equiv) in DMF and water under O_2 gas atmosphere heated at 110 °C for 10 min.[12]

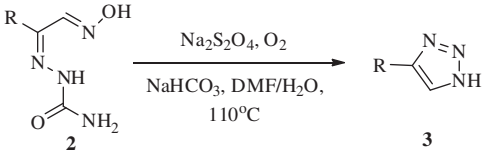
According to the end product, a plausible mechanism for the formation of the products is shown in Scheme 3. Firstly, the isourea **4** was formed at 110 °C from the semicarbazide derivative **2** with the urea-like structure (shown in dashed circle).[13] The isourea intermediate **4** is relatively stable due to the formation of the conjugated system (shown in dashed circle). Under the oxidation–reduction of O_2 and $Na_2S_2O_4$, the imine onium ion **6** was synthesized from the aldoxime, followed by the cyclization reaction which did not obey the Baldwin's rule.[14] Here, $Na_2S_2O_4$ firstly reacted with O_2, and then converted the oxime hydroxyl group into a reactive leaving group, facilitating the breaking of the nitrogen–oxygen bond to form an imine onium cation. And decomposed product $NaHSO_4$ will neutralize $NaHCO_3$ to produce water that contributed to basic hydrolysis. Therefore the reaction still can proceed without the addition of water (Table 1, entries 4 and 8, 17), and just the reaction time was prolonged. The generated intermediate **7** was hydrolyzed under alkaline conditions to obtain **3′** when adding the addition of water to accelerate basic hydrolysis. The end-product **3** is more stable than **3′** which is the multitudinous form.

After developing the optimized reaction condition, the scope of this methodology was explored. Thus a comprehensive number of functional groups were compatible with this reaction to prepare the corresponding 4-substituted aryl-1*H*-1,2,3-triazole. The results are shown in Table 2.

As shown in Table 2, various substrates with both electron donating and withdrawing groups that patterned on the benzene ring gave the corresponding products in good to excellent yields (Table 2, entries 2–12). Particularly, compound **3l** containing heteroaromatic rings also gave its corresponding products with a good yield (Table 2, entry 12). Through the above comparison yields, it can be seen that the method has well tolerated for different aromatic rings

In summary, we have developed an advanced methodology for the one-pot synthesis of 4-substituted aryl-1*H*-1,2,3-triazole in good to excellent yields. In addition, such products will be helpful for the synthesis of natural products and bioactive molecules having pharmaceutical importance. The bio-activity test of some compounds is in progress.

Table 2
One-pot synthesis of various substances



2 **3**

Entry	Substance(R-)	Product	Time[b] min	Yield[c] (%)
1	Ph	**3a**	10	98
2	4-Chlorophenyl	**3b**	12	88
3	4-Nitrophenyl	**3c**	15	81
4	4-Fluorophenyl	**3d**	10	85
5	*p*-Tolyl	**3e**	15	83
6	4-Cyanphenyl	**3f**	15	79
7	3-Chlorophenyl	**3g**	10	80
8	2-Fluorophenyl	**3h**	14	69
9	*o*-Tolyl	**3i**	10	88
10	3,5-Bis(trifluoromethyl)phenyl	**3j**	10	87
11	2-Naphthyl	**3k**	13	85
12	2-Furan	**3l**	20	79

[b] Complete reaction time of Substrates.
[c] Isolated yield by column chromatography.

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References and notes

1. For reviews of 1,2,3-triazoles see: Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1996; Vol. 4, pp 1–126.
2. (a) Chabre, Y. M.; Roy, R. *Curr. Top. Med. Chem.* **2008**, *8*, 1237; (b) Colombo, M.; Peretto, I. *Drug Discovery Today* **2008**, *13*, 677; (c) Hanselmann, R.; Job, G. E.; Johnson, G.; Lou, R. L.; Martynow, J. G.; Reeve, M. M. *Org. Process Res. Dev.* **2010**, *14*, 152; (d) Moumne, R.; Larue, V.; Seijo, B. *Org. Biomol. Chem.* **2010**, *8*, 1154.
3. Buckley, B. R.; Heaney, H. In *Top. Heterocycl. Chem.*; Maes, B. U. W., Ed.; Springer: New York, 2012.
4. (a) Kallander, L. S.; Lu, Q.; Chen, W. T. *J. Med. Chem.* **2005**, *48*, 5644; (b) Röhrig, U. F.; Awad, L.; Grosdidier, A. *J. Med. Chem.* **2010**, *53*, 1172.
5. For recent reviews about Rufinamide. see: (a) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627; (b) Pitlik, J.; Jászberényi, J. C. *J. Heterocycl. Chem.* **1989**, *26*, 461; (c) Rene, M. EP. Patent 0,199,262, 1986.
6. For reviews about the AAC reaction, see: (a) L'Abbe, G. *Chem. Rev.* **1969**, *69*, 345; (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; (c) Sha, C. K.; Mohanakrishnan, A. K. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; p 623.
7. Yap, A. H.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3035.
8. For the preparation of TSE-N_3, TMS-N_3, MeOPEG-N_3, azidomethyl pivalate, azidomethyl morpholine-4-carboxylate and azidomethyl *N,N*-diethylcarbamate, see: (a) T. Jin, S. Kamijo and Y. Yamamoto, *Eur. J. Org. Chem.* 2004, 3789–3791; (b) Molteni, G.; Buttero, P. D. *Tetrahedron* **2005**, *61*, 4983; (c) Loren, J. C.; Krasiński, A.; Fokin, V. V.; Sharpless, K. B. *Synthesis* **2005**, *18*, 2847–2850; (d) Eszter, T.; Andrea, S.; Denes, G.; Gabor, B. *Am. J. Physiol.* **2013**, *304*, 207.
9. For β-bromostyrene, 1,1-dibromoalkenes, anti-3-aryl-2,3-dibromopropanoic acids, nitrostyrene used in this area, see: (a) Barluenga, J.; Valdés, C.; Beltrán, G.; Escribano, M.; Aznar, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 6893; (b) Wang, X. K.; Kuang, C. X.; Yang, Q. *Eur. J. Org. Chem.* **2012**, 424; (c) Jiang, Y. B.; Kuang, C.

X.; Yang, Q. *Synthesis* **2010**, *24*, 4256; (d) Sire, B. Q.; Zard, S. Z. *Synthesis* **2005**, *19*, 3319.
10. All known compounds with data extracted from: (a) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171–3174; (b) Zhang, W. S.; Kuang, C. X.; Yang, Q. *Synthesis* **2010**, *2*, 283–287.
11. Trust, R. I.; Albright, J. D.; Lovell, F. M.; Perkinson, N. A. *J. Heterocycl. Chem.* **1979**, *16*, 1393.
12. *General procedure for the synthesis of* **3b**: To a solution of **2b** (300 mg, 0.25 mmol) in dimethylformamide (5 ml) at 110 °C was added solid sodium hydrogen carbonate (489 mg, 1 mmol) under the O_2 gas atmosphere. The mixture was stirred vigorously for 5 min; solid sodium dithionite (508 g, 0.5 mmol) was added and the mixture was still stirred vigorously for 5 min, followed by water (3 mL) which is used to accelerate basic hydrolysis. Gas evolution took place immediately after the addition of the water. Stirring was continued at 110 °C. After completion of the reaction, the reaction mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel and hexane/EtOAc as eluent. Spectral data for the representative compound **3b**: White needles; yield 84%; mp 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.964 (1H, s), 7.77 (2 H, d, J = 8.4 Hz), 7.40 (2H, d, J = 8.4 Hz); ESI-MS: m/z = 180.03[M+H]$^+$.
13. Ongley, P. A. *Trans. R Soc. NZ* **1948**, *77*, 10–12.
14. (a) Arseniyadis, S.; Huang, P. Q.; Morellet, N. *Heterocycles* **1990**, *31*, 1789–1799; (b) Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron* **1999**, *55*, 13471; (c) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H. P. *Org. Synth.* **1991**, *70*, 54.