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Efficient Synthesis of 1,3,5-Trisubstituted (Pyrrol-2-yl)acetic Acid Esters via Dual Nucleophilic Reactions of Sulfonamides or Carbamate with 4-Trimethyl-siloxy-(5*E*)-hexen-2-ynoates: Lewis Acid Catalyzed S_N1 and Intramolecular Michael Addition

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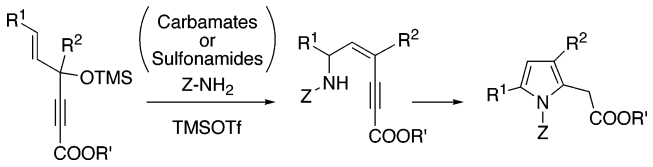
ABSTRACT



Carbamates or sulfonamides have proven to regioselectively attack 2-propynyl-allyl hybrid cations, generated by the action of TMSOTf on 4-(trimethylsioxy)hex-5-en-2-ynoates, to afford conjugated 6-aminohex-4-en-2-ynoates in which an intramolecular amino-Michael reaction took place, leading to pyrrole frameworks. In particular, the sulfonamides gave 1-sulfonylpyrroles in one pot.

Because of their important roles in nature[1] and broad utility in both pharmaceuticals[2] and materials science,[3] pyrroles have been among the most attractive molecules in chemistry and biology. Such characteristics have made the molecules significant synthetic targets and, therefore, have continued to give chemists incentive in exploring novel methods for their preparations.[4] However, with regard to general methods for synthesizing (pyrrol-2-yl)acetic acid esters in one step, only two methods leading to 1,3,4-trisubstituted derivatives have been available.[5] This strongly motivated us to approach the synthesis of pyrroles of this class, and we have succeeded in realizing one-pot preparation of 1,3,5-trisubstituted (pyrrol-2-yl)acetic acid esters (**3**) from 4,6-disubtituted ethyl 4-trimethylsiloxy-5-hexen-2-ynoates (**1**)[6] and sulfonamides (**2**) by the action of catalytic trimethylsilyl trifluoromethanesulfonate (TMSOTf, 20 mol %; CH_2Cl_2; −30 °C to rt; 1−3 h) (Scheme 1). The process involves the formation of 2-propynyl-allyl hybrid cations (**I**$_1$) that undergo S_N1 reaction attacking **2** with exclusive geometrical and regiochemical selectivity to result in the formation of 6-sulfonylamido-(4*Z*)-hexen-2-ynoates (**5**). Because of their convenient spatial arrangement, **5** can smoothly undergo Michael addition to

(1) (a) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison-Wesley Longman: Essex, 1997; pp 192−209. (b) Joule, J. A.; Mills, K. *Heteocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000; pp 237−272. See also, e.g.: Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243.

(2) For blockbuster drugs of substituted pyrroles, see, e.g.: Thompson, R. B. *FASEB J.* **2001**, *15*, 1671−1675. See also refs 14 and 15.

(3) For a recent review, see, e.g.: Jeppesen, J. O.; Becher, J. *Eur. J. Org. Chem.* **2003**, 3245−3266.

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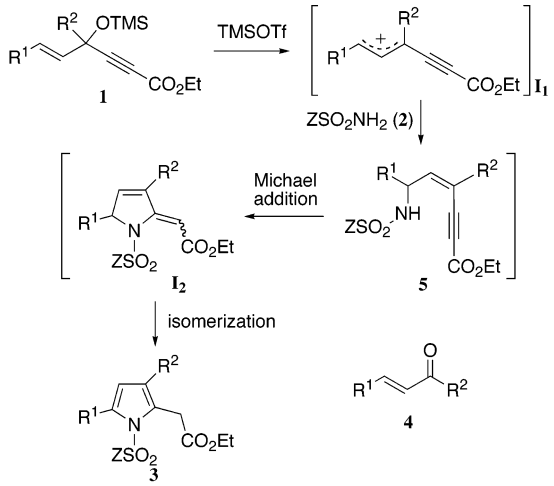
Scheme 1



1a: R^1 = Ph; R^2 = Me
1b: R^1 = Ph; R^2 = *i*-Pr
1c: R^1 = Ph; R^2 = Ph
1d: R^1 = 2-BrPh; R^2 = *i*-Pr
1e: R^1 = Ph; R^2 = 3,4-$(MeO)_2$Ph
1f: R^1 = 4-MeOPh; R^2 = *i*-Pr
1g: R^1 = 4-ClPh; R^2 = *i*-Pr
1h: R^1 = c-C_6H_{11}; R^2 = 4-MeOPh
1i: R^1 = c-C_6H_{11}; R^2 = Ph
1j: R^1 = c-C_6H_{11}; R^2 = Me

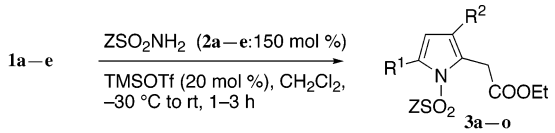
2a: Z = Ph; **2b**: Z = 4-MePh; **2c**: Z = 4-MeOPh; **2d**: Z = 4-NO_2Ph
2e: Z = Me

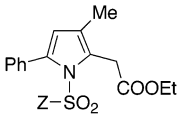
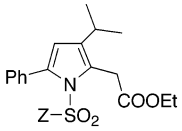
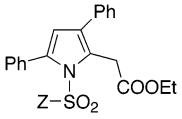
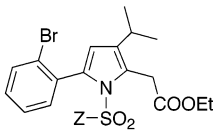
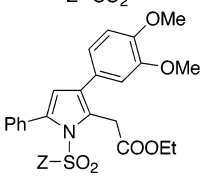
the second products ($\mathbf{I}_2$) followed by facile isomerization resulting with **3**. Because **1a**−**j** were readily prepared by the reaction of enones **4** and lithium acetylide of ethyl propiolate followed by silylation with very high R^1 or R^2 tolerance,[7] the requisite preparation of **1** did not impose any problem on the whole process.

The use of **2** as an *N*-nucleophile is a crucial choice. This *N*-nucleophile would surely be attacked by the highly reactive cation $\mathbf{I}_1$ but should not deactivate the Lewis acid employed for cation generation. Furthermore, after being embedded in **5**, the nitrogen atom must exert enough nucleophilicity to make the following intramolecular Michael addition possible to give the second intermediate $\mathbf{I}_2$. A sulfonyl group in **2** plays an important role in this context. It would reduce the nitrogen Lewis basicity and increase the acidity of the N−H bond in **5**, which is responsible for the appropriateness of **2** as a dual nucleophile in this process. Indeed, normal primary amines or carboxamides were totally ineffective in this transformation, probably as a result of the deactivation of the catalyst TMSOTf by their strong Lewis basicity. When benzyl carbamate was used in place of **2**, S_N1-type amination took place but the expected Michael addition was not effected at all (vide infra) probably because of lack of requisite N−H acidity.

Thus, combinations of **1a**−**e** and **2a**−**e**[8] led to a variety of (pyrrol-2-yl)acetic acid esters (**3a**−**o**) as summarized in Table 1. As mentioned above, the olefinic geometries in **5** are required to be *Z* for the ensuing conjugated addition to occur. In the case of benzyl carbamate the reaction stopped at the stage of S_N1 to give (*Z*)-6-(*N*-cbz)amino-4-hexen-2-

Table 1. One-Pot Pyrrole Synthesis



entry	1	2	pyrrole **3** (yield %)		
1	**1a**	**2a**		**3a**: Z = Ph	(55)
2		**2b**		**3b**: Z = 4-MePh	(81)
3		**2c**		**3c**: Z = 4-MeOPh	(52)
4	**1b**	**2a**		**3d**: Z = Ph	(62)
5		**2b**		**3e**: Z = 4-MePh	(69)
6		**2c**		**3f**: Z = 4-MeOPh	(72)
7		**2e**		**3g**: Z = Me	(39)
8	**1c**	**2a**		**3h**: Z = Ph	(96)
9		**2b**		**3i**: Z = 4-MePh	(89)
10		**2c**		**3j**: Z = 4-MeOPh	(94)
11		**2d**		**3k**: Z = 4-NO_2Ph	(31)
12		**2e**		**3l**: Z = Me	(64)
13	**1d**	**2a**		**3m**: Z = Ph	(71)
14		**2b**		**3n**: Z = 4-MePh	(59)
15	**1e**	**2c**		**3o**: Z = 4-MeOPh	(45)

(4) For recent leading references of pyrrole synthesis using alkyne derivatives, see: (a) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664−5667. (b) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260−9266. (c) Ohri, R. V.; Radosevich, A. T.; Hrovat, K. J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, F. D. *Org. Lett.* **2005**, *7*, 2501−2504. (d) Tejedor, D.; González-Cruz, D.; García-Tellado, F.; Marrero-Tellado, J. J.; Rodríguez, M. L. *J. Am. Chem. Soc.* **2004**, 126, 8390−8391. (e) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957−2960. (f) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468−469. (g) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853−7861. (h) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681−2684. (i) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98−101. (j) Yoshida, M.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2003−2008. (k) Gabriele, B.; Dalerno, G.; Fazio, A.; Campana, F. B. *Chem. Commun.* **2002**, 1408−1409. (l) Kel'in, A. V.; Srmek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075. (m) Lee, C.; Yang, L.; Hwu, T.; Feng, A.; Tseng, V.; Luh, T. *J. Am. Chem. Soc.* **2000**, *122*, 4992−4993.

(5) See refs 4d and 4j; ref 4k is also concerned with (pyrrol-2-yl)acetic acids synthesis, which however required several steps.

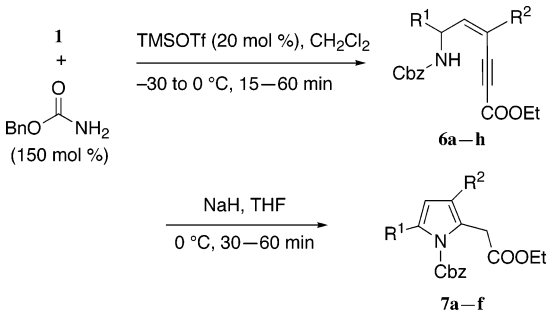
(6) For a series of research concerned with this system, see: (a) Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem.* **2001**, *66*, 4635−4642. (b) Ishikawa, T.; Aikawa, T.; Mori, Y.; Saito, S. *Org. Lett.* **2003**, *5*, 51−54. (c) Ishikawa, T.; Aikawa, T.; Mori, Y.; Saito, S. *Org. Lett.* **2004**, *6*, 1369−1372. (d) Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* **2004**. *6*, 2361−2364.

(7) Ten substrates (**1a**−**j**) were prepared as follows: to a solution of ethyl propiolate in THF was added BuLi at −78 °C, and the mixture was stirred at that temperature for 15 min. To this mixture was added enone at −78 °C followed by stirring at −78 − 0 °C for 4.5 h. After the usual workup, the alcohol product was purified by column chromatography and silylated in the usual way (TMS-Cl, imidazole, THF, 0 °C to rt, 0.5 h) to give **1**, which was purified by column chromatography prior to use. The % yields of **1** depended on the structure of enones. For the experimental detail and spectroscopic data, see Supporting Information.

(8) These sulfonamides are commercially available.

ynoates (**6a**−**f**) (Table 2) in which such stereochemical outcomes were observed with perfect (*Z*)-control without exception.[9]

Table 2. Carbamate as a Nucleophile: Two-Step Pyrrole Synthesis



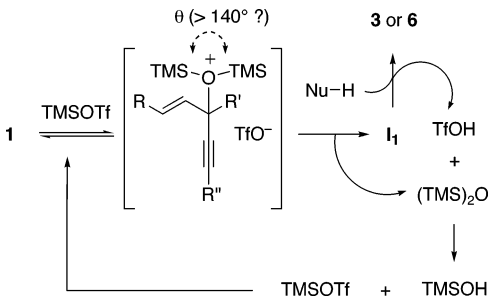
entry	**1**	**6** (yield)	**7** (yield %)
1	**1a**	**6a** (53)	**7a**: R^1 = Ph; R^2 = Me (87)
2	**1b**	**6b** (58)	**7b**: R^1 = Ph; R^2 = *i*-Pr (96)
3	**1c**	**6c** (82)	**7c**: R^1 = Ph; R^2 = Ph (75)
4	**1f**	**6d** (86)	**7d**: R^1 = 4-MeOPh; R^2 = *i*-Pr (94)
5	**1g**	**6e** (57)	**7e**: R^1 = 4-ClPh; R^2 = *i*-Pr (78)
6	**1h**	**6f** (53)	**7f**: R^1 = *c*-C_6H_{11}; R^2 = 4-MeOPh (53)
7	**1i**	**6g** (9)	− (R^1 = *c*-C_6H_{11}; R^2 = Ph)
8	**1j**	**6h** (−)	− (R^1 = *c*-C_6H_{11}; R^2 = Me)

The data in Table 2 clearly indicate some limitations of the present transformation. If R^1 is an aryl group, R^2 is allowed to be an aryl or aliphatic group (entries 1−5), whereas if R^1 is an aliphatic group, R^2 must be an aryl group bearing an electron-donating substituent on the ring (entries 6 and 7). When both R^1 and R^2 groups are aliphatic (entry 8), desilylated substrate was recovered as an alcohol. Although, unlike sulfonylamides, the (*N*-cbz)amino group did not have enough nucleophilicity to attack the conjugated triple bond, the desired transformation smoothly took place to afford (*N*-cbz)pyrroles (**7a**−**f**) in acceptable yields on treatment with NaH in THF (Table 2).

Not only an S_N1 strategy other than S_N2[10] but also the use of *N*-nucleophiles of low Lewis basicity such as **2** or benzyl carbamate should be a key to success for synthesizing **5** or **6**. The less sterically demanding nature of an alkyne group, as well as observed regiochemistry-controlling ability of $\mathbf{I}_1$ in terms of the position of highest positive charge density,[11] would be responsible for the construction of the conjugated 1-amino-(2*Z*)-en-4-yne framework, the requisite for successful ensuing intramolecular Michael addition and thus for the accomplishment of the whole pyrrole synthesis.

It should be also mentioned that the involvement of a TMS ether in **1** may be crucial for the generation of $\mathbf{I}_1$ intermediate (Scheme 1). When a trimethylsilyl cation released from the catalyst can coordinate to the oxygen atom of **1** to which a TMS group attaches, a $(CH_3)_3Si\text{-}O\text{-}Si(CH_3)_3$ bond can be temporally generated with a bond angle of around 140° or more (Scheme 2) judging from reported bond angle value (144°) of disiloxane ($H_3Si\text{-}O\text{-}SiH_3$).[12]

Scheme 2



Such a situation would result in an increase in the more sterically demanding nature of the 1,1,1,3,3,3-hexamethyldisiloxane (HMDSLOX) unit for the thus-generated oxonium ion intermediate shown in Scheme 2, and thus the leaving group ability of the HMDSLOX unit would become enough to generate $\mathbf{I}_1$ under the given reaction conditions. On the other hand, the thus-released HMDSLOX molecule has very low nucleophilicity in a general sense[13] so that $\mathbf{1}_1$ could not return to **1** any more. The reaction of $\mathbf{I}_1$ with nucleophiles leads to **3** or **6** accompanied by the formation of TfOH, which might partly play a role of generating $\mathbf{I}_1$ by protonation. The contribution of this kind, however, might be very low because extremely low yield of **3h** was observed when TfOH was used in place of TMSOTf though it could not completely be ruled out. Rather importantly we should recognize that the HMDSLOX thus-released play a significant role to regenerate the catalyst (TMSOTf) through the reaction with TfOH, leaving behind trimethylsilanol as a byproduct which may be so less nucleophilic that can attack $\mathbf{I}_1$: no formation of products such as a conjugated 1-(trimethylsiloxy)enyne [an enyne product with a TMSO-substituent in place of a $RSO_2N(H)$- or (cbz)N(H)-group in **5** or **6**] was observed.

In summary, we have developed a novel, metal-free, Lewis acid catalyzed synthesis of 1,3,5-trisubstituted (pyrrol-2-yl)-acetic acid esters **3** and **7** from commercially available inexpensive compounds of structural diversity. A series of reactions involving TMSOTf coordination to **1**, generation of $\mathbf{I}_1$, an S_N1 process, and intramolecular Michael addition is kinetically tuned to proceed in a one-pot process. We can use readily available enones, propiolate esters, and aryl- (or alkyl-) sulfonamides or benzyl carbamate as starting com-

(9) For discussion about stereocontrol of this kind, see ref 6.

(10) It used to be the case that the synthesis of (*Z*)-(2-en-4-ynyl)amines similar to **5** or **6** involved bromination (PBr_3) of the corresponding (*Z*)-2-en-4-yn-1-ols and subsequent S_N2 reactions with amines or Mitsunobu reactions of the alcohols. In addition, the syntheses of the alcohols were specified to individual methods according to both kind and position of desired substituents: Koerner, M.; Rickborn, B. *J. Org. Chem.* **1989**, *54*, 9−10.

(11) Elucidation of the exact nature of the observed exclusive regioselectivity of this S_N1 process must wait for future studies.

(12) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697−703 and references cited therein.

(13) For discussion about the lower basicity of disiloxane, see ref 12 and references therein.

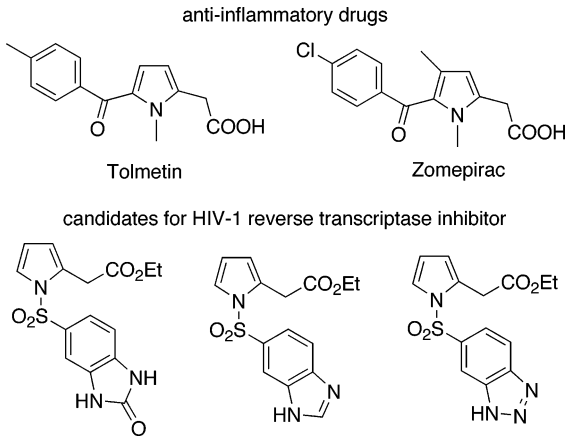


Figure 1. Examples of (pyrrol-2-yl)acetic acid derivatives including those bearing arenesulfonyl groups on the nitrogen atom: anti-inflammatory drugs and candidates for anti-HIV drugs.

ponents. As shown in Figure 1, both tolmetin and zomepirac are typical (pyrrole-2-yl)acetic acid derivatives and are known as an anti-inflammatory drugs[14] that are clinically useful. Some pyrroles also shown in Figure 1 are (pyrrole-2-yl)acetic acid derivatives bearing arenesulfonyl groups on the nitrogen atom and have been known to exert anti-HIV activity as non-nucleoside, reverse transcriptase inhibitors.[15] Therefore, it is no exaggeration to say that the present synthetic method deserves consideration when we contemplate the synthesis of (pyrrol-2-yl)acetic acid esters because it offers vast opportunities commensurate with modern synthetic criteria with respect to structural diversity[16] and chemical efficiency.[17]

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Representative experimental procedures, physical properties and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For clinically useful pharmaceuticals featuring (pyrrol-2-yl)acetic acid, see: Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. In *Pharmaceutical Substances*, 3rd ed.; Thieme: Stuttgart, New York, 1999.

(15) Some 1-sulfonylryrroles exert anti-HIV activity as non-nucleoside, reverse transcriptase inhibitors. See: (a) Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; Colla, P. L. *J. Med. Chem.* **1996**, *39*, 522−530 and references therein. (b) Silvestri, R.; Artico, M.; Martino, G. D.; Novellino, E.; Greco, G.; Lavecchia, A.; Massa, S.; Loi, A. G.; Doratiotto, S.; Piras, G.; Colla, P. L. *Bioorg. Med. Chem.* **2000**, 2305−2309.

(16) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.

(17) Trost, B. M. *Science* **1991**, *254*, 1471−1477.