Tetrahedron Letters 54 (2013) 4693–4696

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A three-component reaction between 1-substituted-2-methylimidazoles, cyanophenylacetylene, and various aldehydes: stereoselective synthesis of (*Z*)-(2-cyano-1-phenyl)vinyl ethers of 2-(2-hydroxyalkyl)imidazoles

Boris A. Trofimov *, Ludmila V. Andriyankova, Lina P. Nikitina, Kseniya V. Belyaeva, Anastasiya G. Mal'kina, Andrei V. Afonin, Igor' A. Ushakov

A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., 664033 Irkutsk, Russian Federation

ARTICLE INFO

Article history:
Received 12 February 2013
Revised 6 June 2013
Accepted 21 June 2013
Available online 29 June 2013

Keywords:
Acetylene
Aldehydes
Imidazoles
Zwitterionic intermediates
Multicomponent reactions

ABSTRACT

A three-component reaction between 1-substituted-2-methylimidazoles (1-Me, Bn), cyanophenylacetylene, and aliphatic (Me, *i*-Pr, *n*-Bu) and aromatic (Ph, 4-CN-, 4-O_2N-C_6H_4) aldehydes occurs without a catalyst or solvent at room temperature (20–25 °C) to afford stereoselectively (*Z*)-(2-cyano-1-phenyl)vinyl ethers of 2-hydroxyalkylimidazoles in 26–57% yields.

Imidazole-based pharmaceuticals such as cimetidine (an inhibitor of gastric acid secretion), etomidate (an anesthetic), ketoconazole (an antifungal medication),[1–3] eprosartan and losartan (antihypertensives), and metronidazole (a chemotherapeutic)[4] are used widely. A number of imidazole derivatives exhibit antithrombic,[5] antiproliferative,[6] antihelminthic, antitumor, fungicidal, and anti-inflammatory[7,8] properties. Thus, significant efforts have been focused on the development of new synthetic approaches for imidazole ring functionalization.

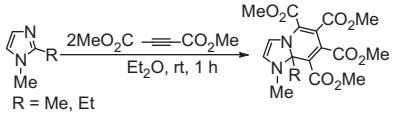
Reactions between imidazoles and electron-deficient acetylenes proceeding via zwitterionic or carbene intermediates have attracted growing attention[9–29] as simple and short routes to various functionalized imidazoles. The key step of these reactions is proton abstraction from position 2 of the imidazole by the anion of the initial zwitterion to generate carbene-like species, which is further intercepted by an appropriate electrophile. However, similar proton abstraction from a methyl group, located at position 2 of the imidazole ring, in the presence of electron-deficient acetylenes, remains hitherto unknown.

The reactions of 1-methyl-2-alkyl-substituted imidazoles with dimethyl acetylenedicarboxylate (DMAD) proceed via annelation of two molecules of DMAD at C-2, while methyl or ethyl substitutents remained intact[30,31] (Scheme 1).

The alkenylation of 1,2-dimethylimidazole with dipropylacetylene at position 5 in the presence of $Ni(cod)_2$/$PCyp_3$/$AlMe_3$[32] or $Ni(cod)_2$/*i*-Pr_3P/Ph-Zn-Ph[33] has been reported.

In contrast, for 1,2-dimethylimidazoles, a limited number of reactions involving deprotonation of the 2-methyl group are known.[34–38] They include the condensation with benzaldehyde under the action of BuLi[34] or aroyl chlorides in the presence of Et_3N,[35] as well as the three-component reaction between 1,2-dimethylimidazole, carbamoyl chloride and benzaldehyde.[36] Also, 1-methyl-2-alkylimidazoles add via the 2-alkyl group to the C=N bond of *N*-tosylimine in the presence of Boc_2O.[37] Hydroxymethylation of 1,2-dimethylimidazole at the 2-methyl group using paraformaldehyde has also been described.[38]

These results prompted us to investigate the reactivity of the 2-methyl group of 1-substituted-2-methylimidazoles **1a**,**b** in a



Scheme 1. The annelation of 1-methyl-2-alkyl-substituted imidazoles with 2 equiv of DMAD.

* Corresponding author. Fax: +7 395 2 41 93 46.
E-mail address: boris_trofimov@irioch.irk.ru (B.A. Trofimov).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.06.095

three-component reaction with cyanophenylacetylene (**2**) and aldehydes **3a–f**. The hope was that the initial zwitterions, the adducts of the imidazoles with acetylene **2**, would be able to abstract a proton from the 2-methyl group, and that the new methylene-centered carbanion would be intercepted by aldehydes as electrophiles.

This preliminary communication reports that the above reaction sequence takes place to lead stereoselectively to (*Z*)-(2-cyano-1-phenyl)vinyl ethers of 2-hydroxyalkylimidazoles, that is, (*Z*)-(imidazol-2-yl)organylethoxypropenenitriles **4a–h**, in 26–57% yields (Table 1). The reaction conditions were mild: no catalyst or solvent was required with the reaction occurring at room temperature. Molar ratio of the reactants **1**:**2**:**3** was 1:1:1, except for the experiments with ethanal (**3a**) which was used in three-fold excess. The conversions of the starting imidazoles ranged from 33% to 100%. The individual *Z*-stereoisomers of vinyl ethers **4a–h** were isolated by column chromatography (neutral Al_2O_3, chloroform/benzene/ethanol, 20:4:1, as eluent). Along with these products, oligomers of the same 1:1:1 composition were eluted in 4–29% yields, while some other oligomers, presumably those of starting acetylene **2**, remained on the adsorbent.

The structures of vinyl ethers **4** were proved unambiguously by ^{1}H, ^{13}C, ^{15}N NMR, 2D (NOESY), and IR spectroscopy.

In the ^{1}H NMR spectra of vinyl ethers **4a–h**, the alkene proton (H-10) was present as a singlet in the region 4.63–4.82 ppm, the two methylene protons at C-6 were observed as a doublet of doublets at 2.90–3.13 and 3.04–3.43 ppm. In the ^{13}C NMR spectra, the carbons of the alkene fragment resonated in the regions 78.7–84.6 (C-10) and 171.1–172.7 (C-9) ppm, and the carbon of the CN-moiety was detected at 116.1–116.7 ppm. Signals for the methyl group at position 2 of the imidazole ring (**1a**,**b**) were absent in the ^{1}H and ^{13}C NMR spectra. This supports the fact that the C(2)-Me group of the starting imidazole **1** participates in the reaction. The ^{15}N NMR spectrum (compound **4g**, R^1 = Bn, R^2 = Me) contained the following signals: −211.0 (N-1), −123.5 (N-3), and −120.2 ppm (nitrogen atom at CN-11).

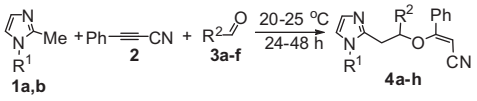
The *Z*-configuration of vinyl ethers **4** was confirmed by 2D NMR spectroscopy (on the example of adduct **4h**, R^1 = Bn, R^2 = Ph). In the NOESY spectrum of vinyl ether **4h**, cross-peaks between the alkene proton (H-10) and the *ortho*-protons of the phenyl substituent at C-9 were observed (Fig. 1).

In the IR spectra of vinyl ethers **4a–h**, absorption bands for the CN, C=C and C–O–C bonds were present at 2214–2216, 1611–1619 and 1078–1098, and 1133–1151 cm^{-1}, respectively.

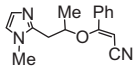
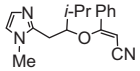
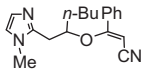
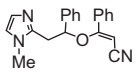
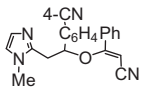
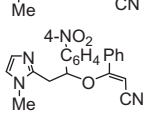
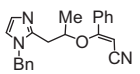
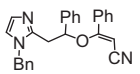
In the ^{1}H NMR and IR spectra of the eluted oligomers, characteristic signals and absorption bands, similar to those of 1:1:1 vinyl ethers **4a–h**, were present, however, they were broad and consisted of several close signals or bands.

Mechanistically, the assembly of vinyl ethers **4a–h** is presumably triggered by zwitterion **A** (Scheme 2), the adduct of imidazole **1** and cyanophenylacetylene (**2**), having the anionic center *trans* to nitrogen (N-3) of the imidazole.[39,40] The next step is proton abstraction from the 2-methyl group by the anionic center of intermediate **A**, to generate CH_2-centered carbanion **B**. Intramolecular proton transfer might be impossible due to the *Z*-configuration of zwitterion **A**. The proton transfer should be facilitated in this case

Table 1
Three-component reaction of 1,2-disubstituted imidazoles **1a**,**b**, cyanophenylacetylene (**2**), and aldehydes **3a–f**



1: R^1 = Me (**a**), Bn (**b**);
3: R^2 = Me(**a**), *i*-Pr (**b**), *n*-Bu (**c**), Ph (**d**), 4-CN-C_6H_4 (**e**), 4-O_2N-C_6H_4 (**f**)

R^1	R^2	Product		Time (h)	Conversion of **1** (%)	Yield[a] (%)
Me	Me		**4a**	24	60	26
Me	*i*-Pr		**4b**	24	66	57
Me	*n*-Bu		**4c**	24	67	26
Me	Ph		**4d**	24	79	30
Me	4-CN-C_6H_4		**4e**	24	100	48[b]
Me	4-O_2N-C_6H_4		**4f**	24	33	26[b]
Bn	Me		**4g**	48	100	49
Bn	Ph		**4h**	48	100	51

[a] Based on consumed imidazole **1**.
[b] MeCN was added to homogenize the reaction mixture.

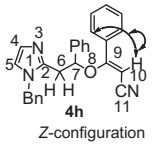
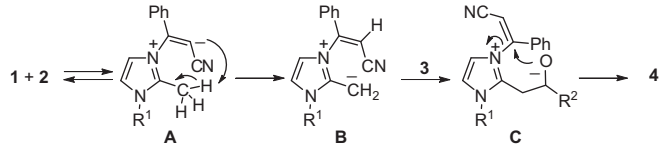


Figure 1. Cross-peaks in the 2D NOESY spectrum of vinyl ether **4h**.



Scheme 2. A plausible mechanism for the three-component assembly of vinyl ethers **4** from imidazoles **1**, cyanophenylacetylene (**2**), and aldehydes **3**.

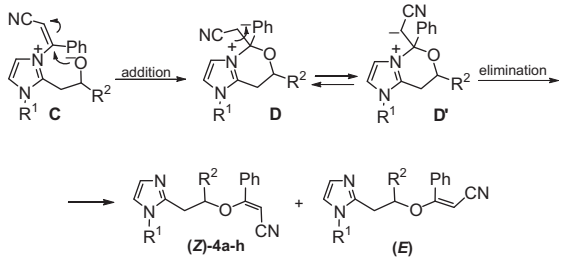
by the enhanced CH-acidity of the 2-methyl group adjacent to the positive charge at the N-3 atom. The intermediate **B** is then intercepted by the aldehyde to give the oxygen-centered zwitterion **C**, which undergoes rearrangement with migration of the positively charged vinyl moiety onto the oxygen anionic center to give vinyl ethers **4a**–**h**. The retention of the *Z*-configuration of the vinyl group implies a concerted character for the migration.

The alternative addition/elimination mechanism (Scheme 3) seems to be less probable, since in this case the stereoselectivity would be compromised due to free rotation about the single C–C bond in the intermediate zwitterion **D**.

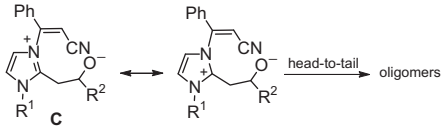
The 1:1:1 oligomer formation may result from oligomerization or cyclooligomerization of intermediate **C** in its resonance form in a head-to-tail manner (Scheme 4).

As previously mentioned, the eluted oligomers, apart from the ^{1}H NMR signals and IR bands being close to those of vinyl ethers **4a**–**h**, contained a C≡N band (2157–2205 cm^{-1}) which is absent in the IR spectra of vinyl ethers **4a**–**h** and may be attributed to the CN vinyl moiety in the oligomers.

In conclusion, a novel method for functionalization of an imidazole ring with an alkyl cyanovinyl moiety, which is able to undergo further transformations has been elaborated. The process is a facile and eco-friendly (catalyst- and solvents-free) three-component reaction between 1-substituted-2-methylimidazoles, cyanophenylacetylene, and aldehydes, the latter including aliphatic and aromatic (with cyano and nitro substituents) examples. The key step is the unprecedented deprotonation of the 2-methyl group by the anionic site of the initial zwitterion (the adduct of the imidazole and cyanophenylacetylene). The products synthesized combine reactive enol, acrylonitrile, and styrene structural units and represent interesting precursors of new imidazole-based drugs.



Scheme 3. An alternative addition/elimination mechanism for the formation of vinyl ethers **4**.



Scheme 4. Possible oligomer formation.

Acknowledgements

This work was supported by leading scientific schools by the President of the Russian Federation (Grant NSh-1550.2012.3), Russian Fund for Basic Research (Grant No. 11-03-00203) and Presidium of the Department of Chemical Sciences and Materials RAS (Grant No. 5.1.3).

Supplementary data

Supplementary data (experimental procedures for the preparation of compounds **4a**–**h** and their spectroscopic characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.095.

References and notes

1. Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571–4624.
2. Sneyd, J. R. *Curr. Pharm. Des.* **2012**, *18*, 6253–6256.
3. Bhattacharyya, A.; Bajpai, M. *Int. J. Pharm. Sci. Nanotechnol.* **2013**, *5*, 1858–1865.
4. Kleeman, A.; Engel, J. In *Pharmaceutical Substances (Syntheses, Patents, Applications)*; Kutscher, B., Reicher, D., Eds.; ; Thieme: Stuttgart, New York, 2001; Vol. 1.
5. Chandra, T.; Brown, K. L. *Tetrahedron Lett.* **2005**, *46*, 8617–8619.
6. Leal, A. S.; Wang, R.; Salvador, J. A. R.; Jing, Y. *Org. Biomol. Chem.* **2013**, *11*, 1726–1738.
7. Gomha, S. M.; Riyadh, S. M.; Abbas, I. M.; Bauomi, M. A. *Heterocycles* **2013**, *87*, 341–356.
8. Narasimhan, B.; Sharma, D.; Kumar, P. *Med. Chem. Res.* **2011**, *20*, 1119–1140.
9. Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665–667.
10. Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopar, L. *Acc. Chem. Res.* **2003**, *36*, 899–907.
11. Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130–5135.
12. Adib, M.; Mollahosseini, M.; Yavari, H.; Sayahi, M. H.; Bijanzadeh, H. R. *Synlett* **2004**, 1086–1088.
13. Nair, V.; Menon, R. S.; Sreekumar, V. *Pure Appl. Chem.* **2005**, *77*, 1191–1198.
14. Nair, V.; Sreekumar, V.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297–2300.
15. Adib, M.; Sheibani, E.; Mostofi, M.; Dhanbary, K.; Bijanzadeh, H. R. *Tetrahedron* **2006**, *62*, 3435–3438.
16. Ma, C.; Ding, H.; Wang, Y. *Org. Lett.* **2006**, *8*, 3133–3136.
17. Yavari, I.; Mirzaei, A.; Moradi, L.; Hosseini, N. *Tetrahedron Lett.* **2008**, *49*, 2355–2358.
18. Trofimov, B. A.; Andriyankova, L. V.; Belyaeva, K. V.; Mal'kina, A. G.; Nikitina, L. P.; Afonin, A. V.; Ushakov, I. A. *J. Org. Chem.* **2008**, *73*, 9155–9157.
19. Trofimov, B. A.; Andriyankova, L. V.; Belyaeva, K. V.; Mal'kina, A. G.; Nikitina, L. P.; Afonin, A. V.; Ushakov, I. A. *Mendeleev Commun.* **2009**, *19*, 42–44.
20. Yavari, I.; Mirzaei, A.; Hossaini, Z.; Souri, S. *Mol. Divers.* **2010**, *14*, 343–347.
21. Xia, E.-Y.; Sun, J.; Yao, R.; Yan, C.-G. *Tetrahedron* **2010**, *66*, 3569–3574.
22. Trofimov, B. A.; Andriyankova, L. V.; Belyaeva, K. V.; Mal'kina, A. G.; Nikitina, L. P.; Afonin, A. V.; Ushakov, I. A. *Eur. J. Org. Chem.* **2010**, 1772–1777.
23. Moafi, L.; Ahadi, S.; Khavasi, H. R.; Bazgir, A. *Synthesis* **2011**, 1399–1402.
24. Trofimov, B. A.; Andriyankova, L. V.; Belyaeva, K. V.; Mal'kina, A. G.; Nikitina, L. P.; Dyachenko, O. A.; Kazheva, O. N.; Alexandrov, G. G.; Shilov, G. V.; Afonin, A. V.; Ushakov, I. A. *Tetrahedron* **2011**, *67*, 1288–1293.
25. Belyaeva, K. V.; Andriyankova, L. V.; Nikitina, L. P.; Ivanov, A. V.; Afonin, A. V.; Ushakov, I. A.; Mal'kina, A. G.; Mikhaleva, A. I.; Trofimov, B. A. *Synthesis* **2011**, 2843–2847.
26. Andriyankova, L. V.; Belyaeva, K. V.; Nikitina, L. P.; Mal'kina, A. G.; Vakul'skaya, T. I.; Khutsishvili, S. S.; Sinegovskaya, L. M.; Trofimov, B. A. *Chem. Heterocycl. Compd.* **2012**, *47*, 1390–1394.
27. Trofimov, B. A.; Andriyankova, L. V.; Belyaeva, K. V. *Chem. Heterocycl. Compd.* **2012**, *48*, 147–154.
28. Trofimov, B. A.; Andriyankova, L. V.; Nikitina, L. P.; Belyaeva, K. V.; Mal'kina, A. G.; Afonin, A. V.; Ushakov, I. A. *Synlett* **2012**, 2069–2072.
29. Belyaeva, K. V.; Andriyankova, L. V.; Nikitina, L. P.; Mal'kina, A. G.; Afonin, A. V.; Trofimov, B. A. *Tetrahedron Lett.* **2012**, *53*, 7040–7043.
30. Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1932**, *498*, 1–49.
31. Crabtree, A.; Johnson, A. W. *J. Chem. Soc.* **1962**, 1510–1512.

32. Kanyiva, K. S.; Löbermann, F.; Nakao, Y.; Hiyama, T. *Tetrahedron Lett.* **2009**, *50*, 3463–3466.
33. Nakao, Y. Hiyama, T. JP Patent 2009091336 A 20090430, 2009; *Chem. Abstr.* **2009**, *150*, 494752.
34. Noyce, D. S.; Stowe, G. T.; Wong, W. *J. Org. Chem.* **1974**, *39*, 2301–2302.
35. Bastiaansen, L. A. M.; Mocco, A. A.; Godefroi, E. F. *J. Chem. Soc., Chem. Commun.* **1974**, 36.
36. Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189–192.
37. Zificsak, C. A.; Hlasta, D. J. *Tetrahedron Lett.* **2005**, *46*, 4789–4792.
38. Nguyen, D. Q.; Bae, H. W.; Jeon, E. H.; Lee, J. S.; Cheong, M.; Kim, H. S.; Lee, H. *J. Power Sources* **2008**, *183*, 303–309.
39. Miller, S. I.; Tanaka, R. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; ; Wiley-Interscience: New York, 1970; Vol. 1, p 143.
40. Dickstein, J. I.; Miller, S. I. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; ; Wiley: New York, 1978; Vol. 2, p 814.