Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 2829–2832

Tetrahedron Letters

Montmorillonite K-10 as a mild acid for the Nicholas reaction

Fernando R. Pinacho Crisóstomo, Romen Carrillo, Tomás Martín and Víctor S. Martín*

Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna C/Astrofísico Francisco Sánchez, 2, 38206 La Laguna, Tenerife, Spain

Received 20 January 2005; revised 16 February 2005; accepted 22 February 2005

Abstract—The use of Montmorillonite K-10 as a convenient acid component in the Nicholas reaction is described. Its use permits functional selectivity, inter- and intramolecular reactions and convenience in the experimental conditions. A four-step one-pot [$Co_2(CO)_6$–acetylene complex formation, THP-removal, cyclization and complex cleavage] process permits the direct synthesis of 2-ethynyl-tetrahydrofuran from 6-(tetrahydro-2*H*-pyran-2-yloxy)hex-1-yn-3-ol.

Since its discovery,[1] the Nicholas reaction has gained great significance as a powerful synthetic tool due to its high versatility and because it enables the introduction of different functional groups. It is for this reason that there have been many applications for this reaction varying both the structure of the cation and the nucleophile.[1c,2] Hitherto, this reaction implied the use of either a protic acid or a Lewis acid, mainly trifluoromethanesulfonic acid, $HBF_4{\cdot}OEt_2$ and $BF_3{\cdot}OEt_2$ (Fig. 1). However, these are unstable and harsh substances and also complicate the application of this reaction to systems with acid-sensitive functionalities. With these facts in mind and taking into account the use lately of clays as acid, we decided to investigate the use of solid materials as the acid source in order to achieve selectivity, mildness and simplicity at the work-up step. After trying different solid acidic materials such as silica gel, Amberlysts,® and Dowex® we found Montmorillonite K-10 to be a mild, effective and safe acid for the Nicholas reaction.

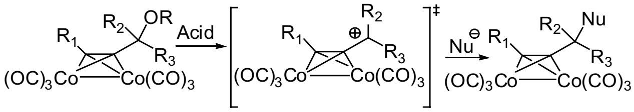


Figure 1. Nicholas reaction.

The use of solid acidic materials such as Montmorillonite clays is very attractive since they can easily be recovered from the reaction mixture by simple filtration and can be reused after activation, thereby making the process economically viable.[3] Montmorillonite K-10 has been reported to promote acid-dependent reactions such as the formation of dimethyl acetals[4] and enamines,[5] as well as Ferrier rearrangements.[6] To the best of our knowledge it has never been employed as an acid in the Nicholas reaction.

The $Co_2(CO)_6$–propargylic complexes used were easily synthesized via nucleophilic addition of the lithium salt of the alkyne to the corresponding aldehyde, and the resulting propargylic alcohols were complexed with $Co_2(CO)_8$. To a solution of $Co_2(CO)_6$–alkyne complex in CH_2Cl_2 or toluene was directly added Montmorillonite K-10. Once the reaction had finished, it was filtered, the alkyne was decomplexed with CAN in acetone, and the crude product purified by chromatographic column.

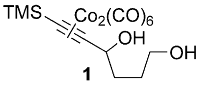
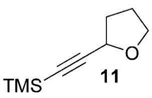
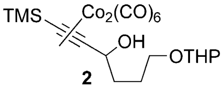
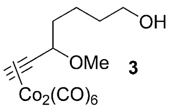
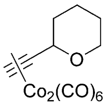
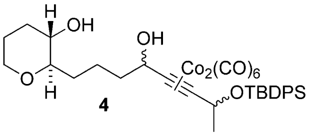
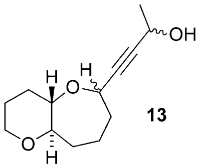
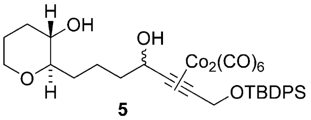
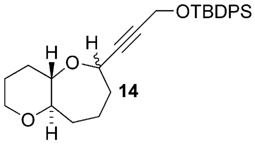
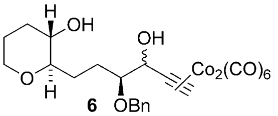
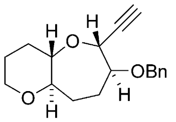
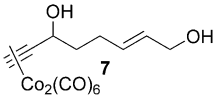
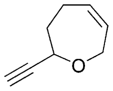
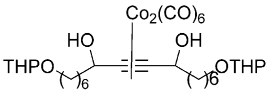
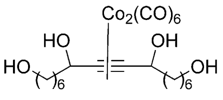
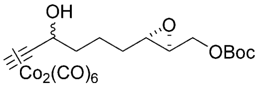
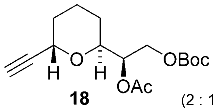
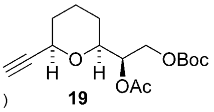
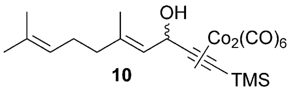
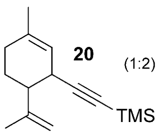
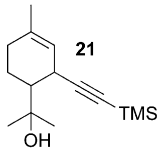
As shown in Table 1, Montmorillonite K-10 effectively promotes the formation of five- and six-membered cyclic ethers (entries 1–3) in very high yields at room temperature although more slowly than does $BF_3{\cdot}OEt_2$. It is worth noting that the presence of a THP-protected alcohol did not imply a significant decrease in the yield. However, it was necessary to use slightly more energetic conditions, such as refluxing dichloromethane or, even better, toluene at 60 °C (entry 2).[7] This fact suggests that Montmorillonite K-10 also favours the tetrahydropyranyl ether cleavage, before promoting the Nicholas reaction.

Keywords: Nicholas reaction; Cyclic ether; Cobalt.

* Corresponding author. Tel.: +34 922318579; fax: +34 922318571; e-mail: vmartin@ull.es

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.02.118

Table 1. Montmorillonite K-10 as the acid component in the Nicholas reaction

Entry	Complex	Product	Method[a] (time)	Yield (%)
1	 **1**	 **11**	A (1 h)	90
2	 **2**	**11**	B (3 h)	85
3[b]	 **3**	 **12**	A (12 h)	90[b]
4	 **4**	 **13**	A (5 h)	67
5	 **5**	 **14**	A (5 h)	78
6	 **6**	 **15**	A or B	—
7	 **7**	 **16**	A or B	—
8	 **8**	 **17**	A (48 h)	65[b]
9	 **9**	 **18** (2 : 1)  **19**	A (24 h) B (3 h)	65
10	 **10**	 **20** (1:2)  **21**	B (16 h)	85

[a] Method A: to a solution of the $Co_2(CO)_6$ complex in CH_2Cl_2 was added Montmorillonite K-10 (three times in weight relative to the complex) and the mixture was stirred until TLC showed the end of the reaction. Then, the mixture was filtered, concentrated, dissolved in acetone and 4 equiv of CAN were added at 0 °C. The reaction mixture was stirred at 0 °C until TLC showed completion of the reaction (ca. 5 min). The mixture was evaporated and the residue diluted with water and extracted with Et_2O. The combined organic solutions were dried ($MgSO_4$), filtered, concentrated and purified by flash column chromatography. Method B: same as method A, but using toluene at 60 °C instead of CH_2Cl_2.

[b] The resulting product was isolated as a $Co_2(CO)_6$ complex.

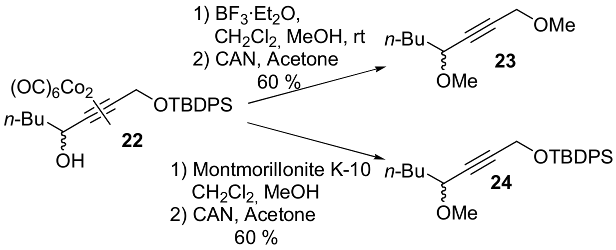
Table 1 also shows that oxepanes could be synthesized from the corresponding hydroxy-alkyne complexes in quite good yields (entries 4 and 5). Surprisingly, **6** was not able to form the corresponding bicyclic product and it does not react even at 60 °C in toluene. Montmorillonite K-10 is unable to isomerize the double bond in **7** to afford cyclization (entry 7), as does $BF_3·OEt_2$.[8]

If the final ring is larger than an oxepane, the Nicholas reaction does not afford cyclic products.[9] Thus, Montmorillonite K-10, as occurs with $BF_3·OEt_2$, is unable to promote the double cyclization of **8**, and only hydroxyl groups are deprotected.

The versatility of the acid could be proven by changing the nature of the nucleophile. Thus, epoxide **9**[10] can also act as a nucleophile affording a cyclic ether at room temperature in CH_2Cl_2. The reaction could be accelerated if toluene at 60 °C was used instead. It should be mentioned that the obtained diastereomeric ratio agrees with that obtained using $BF_3·OEt_2$ at very low temperature (−78 °C). Carbon nucleophiles also work quite well and thus diene **10** leads to carbacycles **20** and **21** (entry 10). The in situ generated tertiary cation can be quenched either by elimination or by water addition, two different products therefore being obtained, and the ratio between them again agrees with that provided by $BF_3·OEt_2$ at low temperature (−20 °C). This similar mode of action between Montmorillonite K-10 and $BF_3·OEt_2$ at low temperature, indicates the smoothness of Montmorillonite K-10 as an acid and it drove us to verify the influence of Montmorillonite K-10 on the matter of regioselectivity in the Nicholas reaction.

As can be seen in Table 1 (entry 4), cyclization of **4** is promoted in good yield by Montmorillonite K-10, but in addition a concomitant deprotection of the other propargylic hydroxyl is produced. This fact demonstrates that both propargylic positions are susceptible of being activated because they are both secondary. The nucleophile attacks the position that provides the seven-membered ring, which is thermodynamically more favoured than the alternative 10-membered ring, whereas the remaining propargylic cation is quenched by water, affording a free hydroxy group. In entry 5 there is an analogous situation, but after cyclization providing a seven-membered ring, the primary silyl ether remained intact. These facts could imply that Montmorillonite K-10 is able to perceive the subtle difference between two propargylic sites, with slight differences in reactivity between them.

When two possible sites exist for the Nicholas reaction, regioselectivity has only been addressed on rare occasions.[11] In order to verify if the Nicholas reaction undergoes regioselectivity with Montmorillonite K-10 a model was proposed. The model employed was **22**, a compound that possesses two propargylic sites, one of them secondary whereas the other one is primary and protected as a silyl ether (Scheme 1). It is easily synthesized from valeraldehyde and the lithium salt of the *tert*-butyl(diphenyl)(2-propynyloxy)silane. In order to determine which propargylic site can be activated, a CH_2Cl_2 solution was treated with either $BF_3·OEt_2$ or Montmorillonite K-10, adding an excess of methanol. The more readily activated site must show a methoxy group at the end of reaction. In fact, the $BF_3·OEt_2$-mediated Nicholas reaction product **23** displayed two methoxy groups at both propargylic sites, whereas the Montmorillonite-mediated reaction selectively distinguishes between two sites and only the nucleophilic attack at the secondary position is enabled to afford **24**, even with very long reaction times (24 h).

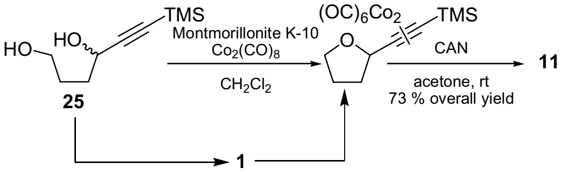


Scheme 1. Selectivity using external nucleophiles.

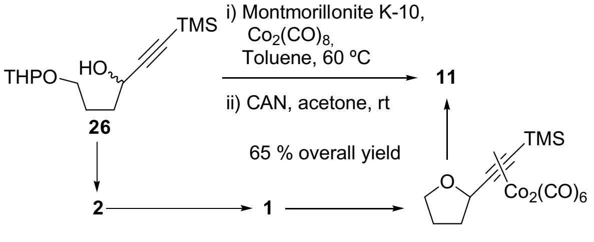
Finally, the extreme smoothness of Montmorillonite K-10 suggested to us the possibility of coexistence between the acid and $Co_2(CO)_8$, permitting a one-pot process combining the in situ alkyne complexation with the Nicholas reaction.

In order to check this possibility when we added Montmorillonite K-10 to a CH_2Cl_2 solution of **25** followed by $Co_2(CO)_8$, cyclized compound **11** was nicely obtained (Scheme 2), with an overall yield of 73%, after alkyne decomplexation with CAN in acetone.

A three-step one-pot process is even possible if **26** is used instead of **25**. It consists of alkyne complexation, THP ether cleavage and finally Nicholas reaction. If acetone and then CAN is added to the reaction mixture, even alkyne decomplexation is successfully achieved in the same reaction flask. Thus decomplexed cyclic ether **11** is directly obtained from the linear alkyne **25** through a four-step one-pot process with an excellent 65% overall yield (Scheme 3).



Scheme 2. Two-step one-pot process.



Scheme 3. Four-step one-pot process.

In summary, Montmorillonite K-10 has been successfully applied as an acid in Nicholas reactions. Its behaviour suggests extreme smoothness, analogous to that observed for $BF_3{\cdot}OEt_2$ at very low temperatures. That smoothness, in addition, allows regioselectivity when two propargylic sites exist. And finally, it enables the one-pot process that consists of alkyne complexation–Nicholas reaction–alkyne decomplexation, followed by a simple filtration at the end of reaction. This opens an exciting possibility in fields such as solid-phase synthesis in which the Nicholas reaction has been used recently, since it would allow not only a one-pot method but would also remove both the remaining resin and the acid used by simple filtration.[12]

Acknowledgements

The authors thank Dr. F. García-Tellado for helpful discussion and the MYCT (PPQ2002-04361-C04-02) of Spain and the Canary Islands Government for supporting this research. F.R.P.C. thanks CajaCanarias for a FPI fellowship. R.C. thanks the Spanish MEC for a FPU fellowship. T.M. thanks the Spanish MCYT-FSE for a Ramón y Cajal contract.

References and notes

1. (a) Nicholas, K. M.; Pettit, R. *J. Organomet. Chem.* **1972**, *44*, C21–C24; (b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207–214; (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809–826; (d) Müller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021–2033; (e) Welker, M. E. *Cur. Org. Chem.* **2001**, *5*, 785–807.
2. Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133–4170.
3. Yadav, J. S.; Subba Reddy, B. V.; Sunitha, V.; Srinivasa Reddy, K.; Ramakrishna, K. V. S. *Tetrahedron Lett.* **2004**, *45*, 7947–7950.
4. Taylor, E. C.; Chiang, C.-S. *Synthesis* **1977**, 467.
5. Hunig, S.; Benzig, E.; Lucke, E. *Chem. Ber.* **1957**, *90*, 2833–2840.
6. (a) de Freitas Filho, J. R.; Srivastava, R. M.; Soro, Y.; Cottier, L.; Descotes, G. J. *Carbohydr. Chem.* **2001**, *20*, 561–568; (b) de Oliveira, R. N.; de Freitas Filho, J. R.; Srivastava, R. M. *Tetrahedron Lett.* **2002**, *43*, 2141–2143; (c) Shanmugasundaram, B.; Bose, A. K.; Balasubramanian, K. K. *Tetrahedron Lett.* **2002**, *43*, 6795–6798.
7. Higher temperature induces a gradual decomposition of complex.
8. We have found that in some cases $BF_3{\cdot}OEt_2$ is able to isomerize *E* to *Z*-double bonds during the ring formation. Unpublished results: Crisóstomo, F. R. P.; Martín, T.; Martín, V. S.
9. Only the presence of a rigid structural motif such as *cis*-double bonds helps cyclization by the Nicholas reaction, see: Betancort, J. M.; Martín, T.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **2003**, *69*, 3216–3224.
10. Crisóstomo, F. R. P.; Martín, T.; Martín, V. S. *Org. Lett.* **2004**, *66*, 565–568.
11. Guo, R.; Gibe, R.; Green, J. R. *Can. J. Chem.* **2004**, 366–374.
12. Cassel, J. A.; Leue, S.; Gachkova, N. I.; Kann, N. C. *J. Org. Chem.* **2002**, *67*, 9460–9463.