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Double Michael addition of azoles to methyl propiolate: a straightforward entry to ligands with two heterocyclic rings

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Dedicated to Dr. Juan Carlos del Amo, deceased on 11 March 2004 Madrid attacks

Abstract—The synthesis of methyl bis(azol-1-yl)propionates is reported for the first time. These bridge-functionalized bis(azol-1-yl)methanes are prepared by a double Michael addition of azoles to methyl propiolate, representing a new methodology for the synthesis of polydentate ligands.

Bis(azol-1-yl)methanes are useful compounds for coordination chemistry due to their behaviour as polydentate ligands. Bis(pyrazol-1-yl)methane, which is able to form *N*,*N*-complexes[1] and bis(imidazol-1-yl)methane, after quaternization and deprotonation, leads to bis-carbenes, which are able to coordinate transition metals.[2] 1,2,4-Triazole ring participates in imidazole and pyrazole possibilities (Chart 1).[3]

Moreover, by functionalization of the methylene bridge, bis(azol-1-yl)methanes may be transformed in (i) bidentate ligands with a focal group, which could be used to built different macromolecules as polymers and dendrimers by using the convergent methodologies for the dendrimer synthesis,[4] and (ii) tridentate ligands, scorpionates[5] and heteroscorpionates[6] when bis(pyrazol-1-yl)methane derivatives are used (Chart 1).

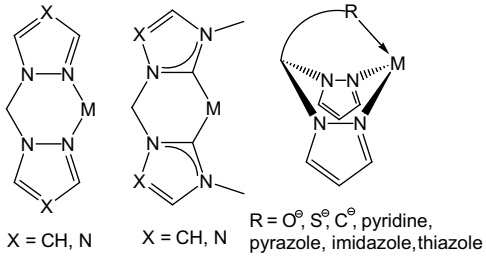

Chart 1.

There are three general synthetic methodologies to the bridge-functionalized bis(azol-1-yl)methanes: (i) the lithiation of 5-substituted-1,1′-methylenedipyrazole followed by reaction with electrophiles;[7] (ii) the reaction of the azole with gem-difunctionalized compounds[8] and (iii) the reaction of carbonyl compounds with 1,1′-carbonylbisazole[9] and 1,1′-sulfinyldipyrazole,[9c,e] and indazole.[10]

Although the Michael addition of azoles to electron-deficient alkenes is an habitual via to azole-substituted esters, lactones, amides, nitriles and ketones,[11] and alkyl acrylates have been obtained by addition to related alkynes,[12] the double Michael addition to alkynes is a not usual reaction. In the best of our knowledge, only one example of double addition of pyrazole to 3-butynone has been reported.[13] Examples of double Michael addition of pyrazoles to DMAD[13] and to quinones[14] have been also reported. Here we report the synthesis of 3,3-bis(imidazol-1-yl)-, 3,3-bis(pyrazol-1-yl)- and 3,3-bis(1,2,4-triazol-1-yl)propionic acid derivatives by a double Michael addition of the azole to methyl propiolate (Scheme 1). This approaches represent a new methodology for the synthesis of bridge-functionalized bis(azol-1-yl)methanes.

Compound **2** was prepared from 1,2,4-triazole by reaction with methyl acrylate in THF using the

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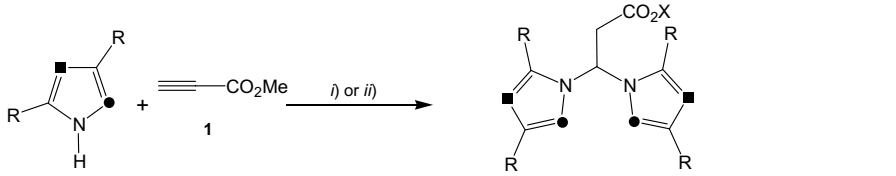

Scheme 1. Reagents and conditions: (i) NaH (50%mol for **2**–**5**, 1.33%mol for **6**), THF, reflux; (ii) $ZnCl_2$ (0.5%mol), MeOH, reflux for compound **7**.

Table 1. Reaction conditions for the synthesis of compounds **2**–**7**[16]

Entry	Azole	AzH/**1**/NaH	Product	Yield (%)
1[a]	1,2,4-Triazole	4/1/2	**2**	83
2[a]	Pyrazole	4/1/2	**3**	65
3[b]	3,5-Dimethylpyrazole	4/1/2	**4**	45
4[a]	Imidazole	4/1/2	**5**	[d]
5[a]	Pyrazole	3/1/0.04	**6**	55
6[c]	Imidazole	2.3/1/0	**7**	44

[a] THF, reflux, 24 h.
[b] THF, reflux, 48 h.
[c] MeOH, 80 °C, 5 days.
[d] Yield not determined.

azole/Michael acceptor/base molar ratio indicated in Table 1.

The use of the appropriate molar ratio (4/1/2) guarantees the presence of both the azolate anion and the azole, the latter of which protonates the resulting enolate. This protonation seems to be necessary to perform the second Michael addition. When a 2/1/2 molar ratio was used the reaction was not complete and the mono-addition compounds were also obtained. These facts point out to a consecutive process in which after the first addition and subsequent protonation of the enolate, the second addition takes place. However, all attempts for synthesize bis(azol-1-yl)propionates by azole addition to β-azolylacrylates, the mono addition products, failed in our hands. We have not got a satisfactory explanation for this observation.

Using the same conditions, pyrazole and imidazole gave sodium propionate salts (**3**–**5**) instead of the expected methyl bis(azol-1-yl)propionates (**6**–**7**). The formation of the salts **3**–**5** is considered to proceed via the nucleophilic attack of the azole to the previously formed ester yielding an azolide intermediary, which is hydrolyzed during the work-up to generate the indicated salts.

Avoiding the use of large quantities of base these methyl propionates can be obtained. Thus, methyl 3,3-bis(pyrazol-1-yl)propionate **6** was prepared using catalytic amount of base. Even, methyl 3,3-bis(imidazol-1-yl)propionate **7** may be obtained in the absence of base, in refluxed methanol activating the Michael acceptor with a catalytic amount of zinc chloride. In these conditions, as indicated above, minor quantities of monoaddition products, in *cis* and *trans* geometry, were detected.

While ester derivatives (**2**, **6** and **7**) are highly soluble in common organic solvents, their counterparts sodium salts (**3**, **4** and **5**) only showed good solubility in water. This drawback avoided a complete purification of **5**. Only an analytical sample of this compound could be obtained after a tedious chromatography.

All new compounds were characterized using various analytical techniques. IR analyses gave the expected bands around 1730 cm^{-1} for esters **2**, **6** and **7**, and 1600 cm^{-1} for the sodium salts derivatives **3**–**5**. ^1H NMR experiments proved very useful to confirm the double Michael addition, which was established on the basis of the presence of a doublet at 3.3–3.7 ppm and a triplet at 6–7 ppm, corresponding to methylene and methyne groups, respectively. Two signals at 37.9–42.1 and 66.1–72.8 ppm in ^{13}C NMR due to methylene and methyne groups,[15] respectively, confirm the structure of the product. Absence of signal around 3.7 ppm in the ^1H NMR spectra and 52.5 ppm in the ^{13}C NMR spectra for the compounds **3**–**5** is indicative of hydrolysis of the ester moiety.

It was also observed that hydrogen atoms in position 2 of the imidazole rings of **5** are acid enough to be completely changed by deuterium when the sample was left for 3 days in D_2O.

In conclusion a new and straightforward access to bridge-functionalized bis(azol-1-yl)methanes is described. The methodology reported may be used with a wide series of azoles and can be envisaged as a new entry to heteroscorpionates, and polymers and dendrimers with heterocyclic moieties.

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15. This assignment was performed by HETCOR experiments.
16. Representative procedure: The azole was deprotonated with sodium hydride in THF for 45 min. Then methyl propiolate was added and the mixture was heated to reflux for the corresponding time. Compound **2**: Reaction time 24 h. The solvent was evaporated under vacuum and the residue was heated at 80 °C for 4 h. The solid was extracted with CH_2Cl_2. Product was recrystallized from toluene. Yield 83%. Mp: 117–118 °C; MS *m/z* (APCI+): 223. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 3.71 (s, 3H), 3.72 (d, J = 7.2 Hz, 2H), 7.09 (t, J = 7.2 Hz, 1H), 7.99 (s, 2H), 8.38 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 37.9, 52.7, 67.9, 143.1, 152.7, 168.0. IR (KBr, cm^{-1}): 1723. Compound **3**: Reaction time 24 h. Reaction crude was filtered and the residue washed with THF. Product was recrystallized from a mixture of EtOH–Et_2O. Yield 65%. Mp: >250 °C. MS *m/e* (ESI−): 205. ^{1}H NMR (D_2O, 500 MHz, δ): 3.33 (d, J = 7.3 Hz, 2H), 6.24 (pseudo-t, J = 2.2 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H), 7.45 (d, J = 1.5 Hz, 2H), 7.76 (d, J = 2.6 Hz, 2H). ^{13}C NMR (D_2O, 125 MHz, δ): 41.0, 72.8, 106.8, 130.3, 141.3, 175.8. IR (KBr, cm^{-1}): 1613. Compound **4**: Reaction time 48 h. Reaction crude was cooled to 0 °C and filtered. The residue washed with cool THF. Product was recrystallized from ethanol. Yield 45%. Mp: >250 °C. MS *m/e* (ESI−): 261. ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 2.04 (s, 6H), 2.33 (s, 6H), 3.03 (d, J = 6.2 Hz, 2H), 5.71 (s, 2H), 6.76 (t, J = 6.4 Hz, 1H). ^{13}C NMR (DMSO, 125 MHz, δ): 11.1, 13.4, 42.1, 70.0, 105.5, 139.1, 145.6, 171.3. IR (KBr, cm^{-1}): 1601. Compound **5**: Reaction time 24 h. The crude mixture was filtered. Only an analytical sample was obtained after gradient column chromatography on silica gel in a mixture of methanol–ethyl acetate 1:3 to 1:0. Mp: >250 °C. MS *m/z* (APCI−): 205. ^{1}H NMR (D_2O, 500 MHz, δ): 2.55 (d, J = 7.7 Hz, 2H), 5.96 (t, J = 7.7 Hz, 1H), 6.19 (s, 2H), 6.49 (s, 2H), 7.11 (s, 2H). ^{13}C NMR (D_2O, 125 MHz, δ): 42.1, 66.1, 118.0, 128.9, 136.8, 175.2. IR (KBr, cm^{-1}): 1595. Compound **6**: Reaction time 24 h. Reaction crude was filtered and the solvent of the liquid layer was evaporated. The residue was washed with ethylic ether and recrystallized from CCl_4. Yield 55%. Mp: 118–119 °C. MS *m/z* (APCI+): 221. ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 3.66 (s, 3H), 3.70 (d, J = 7.3 Hz, 2H), 6.27 (pseudo-t, J = 1.8 Hz, 2H), 6.91 (t, J = 7.3 Hz, 1H), 7.54 (d, J = 1.8 Hz, 2H), 7.58 (d, J = 2.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 38.4, 52.2, 71.7, 106.8, 128.7, 140.4, 169.0. IR (KBr, cm^{-1}): 1732. Compound **7**: A mixture of imidazole, methyl propiolate and $ZnCl_2$, in methanol was refluxed for 120 h. Reaction crude was filtered and solvent of liquid layer evaporated. The residue was washed with cool THF and recrystallized from toluene. Yield 44%. Mp: 136–138 °C. MS *m/z* (APCI+): 221. ^{1}H NMR ($CDCl_3$, 500 MHz, δ): 3.44 (d, J = 7.3 Hz, 2H), 3.71 (s, 3H), 6.71 (t, J = 7.3 Hz, 1H), 7.00 (s, 2H), 7.11 (s, 2H), 7.67 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz, δ): 40.0, 52.8, 64.4, 116.4, 131.1, 135.6, 167.8. IR (KBr, cm^{-1}): 1730.