Tetrahedron Letters 50 (2009) 1196–1198

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Engaging a thiazole-DMAD zwitterion in novel one-pot multicomponent reactions involving chromones. Expeditious synthesis of thiazolo- and chromenothiazolopyridines

Michael A. Terzidis, Julia Stephanidou-Stephanatou *, Constantinos A. Tsoleridis *

Laboratory of Organic Chemistry, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

ARTICLE INFO

Article history:
Received 29 October 2008
Revised 17 December 2008
Accepted 22 December 2008
Available online 8 January 2009

Keywords:
Acetylenedicarboxylate
Chromone-3-carboxaldehydes
Chromenothiazolopyridines
Multicomponent reactions
Thiazolopyridines

ABSTRACT

The 1,4-dipole derived from 4,5-dimethylthiazole and DMAD has been shown to react readily with chromone-3-carboxaldehydes resulting, after an unusual rearrangement, in the facile synthesis of thiazolo[3,2-*a*]pyridine derivatives; in some instances tetracyclic chromenothiazolopyridines were formed.

The pronounced reactivity of nitrogen-containing heterocycles towards dimethyl acetylenedicarboxylate (DMAD) is well documented.[1] The reaction generally involves the formation of a dipolar intermediate between the *N*-heterocycle and DMAD, which undergoes further reactions with external dipolarophiles leading to a variety of heterocyclic compounds.

An example of this type of reaction was established in the pioneering work of Huisgen et al.,[2] who showed that the reaction of isoquinoline and DMAD proceeds through a 1,4-dipolar intermediate, by trapping it with phenylisocyanate, diethyl mesoxalate and dimethyl azodicarboxylate. Except for isolated reports,[3] such reactions nevertheless remain underexploited. Recently, Nair et al.[4] investigated the different reactivity patterns of the isoquinoline-DMAD and pyridine-DMAD zwitterions. Whereas the first engaged exclusively in three-component reactions, the second induced novel molecular rearrangements.[5]

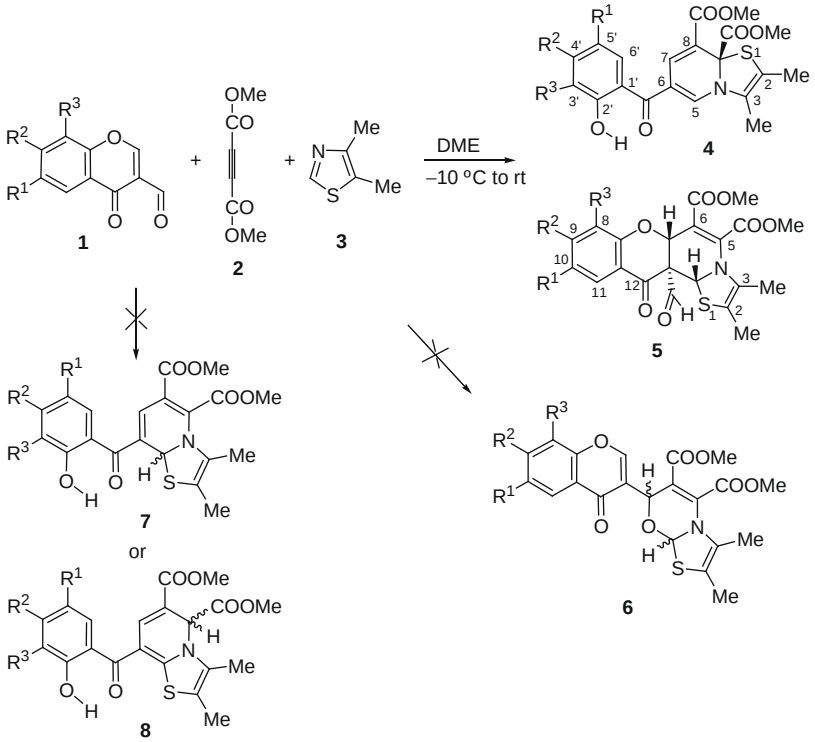
Moreover, it was found that the imidazole-DMAD zwitterion could be involved in one-pot three-component syntheses.[6] In the light of our interest on the development of new routes towards heterocyclic systems,[7] we have exploited the reactivity profile of a thiazole-DMAD zwitterion in bringing about three-component reactions with chromone-3-carboxaldehydes. These compounds represent a very reactive system owing to the presence of an unsaturated keto function, a conjugated second carbonyl group at C-3 and above all a very reactive electrophilic centre at C-2. In addition, since the thiazole ring is able to undergo molecular rearrangment[8] its use would give to the reaction a new perspective.

Our studies began with the reaction of DMAD with chromone-3-carboxaldehyde **1a** and 4,5-dimethylthiazole to afford the thiazolo[3,2-*a*]pyridinedicarboxylate **4a** in 45% yield,[9] instead of the expected chromenylthiazolooxazines **6** or thiazolopyridines **7** (and/or **8**) (Scheme 1). A minor product, identified as chromenothiazolopyridinedicarboxylate **5a** (~4% yield), was also detected. The reaction appears to be general with a number of substituted 3-formyl-chromones affording thiazolo[3,2-*a*]pyridinedicarboxylates **4** in moderate yields. However, in the case of 6-methyl-3-formylchromone (**1b**), **5b** was the main reaction product, whereas **4b** was formed as a minor product in ~5% yield. The results are summarized in Table 1.

Concerning the assignment of **4a**, elemental analysis and MS spectroscopy unequivocally established that reaction of one molecule of chromone-3-carboxaldehyde **1a** with one molecule of dimethylthiazole and one molecule of DMAD with loss of a formyl group had occurred. This fact was also confirmed from the ^{13}C NMR spectrum, where 20 different signals were observed. Moreover, in the IR spectrum the broad absorption at 3458 cm^{-1} indicated a OH group, whereas the two chromone carbonyl absorptions at 1695 and 1650 cm^{-1} were replaced by carbonyl absorptions at 1738 and 1698 cm^{-1}. The carbonyl carbon at 192.8 ppm in combination with a hydrogen bonded hydroxy proton at δ 11.63

* Corresponding authors. Tel.: +30 2310 997831; fax: +30 2310 997679 (J.S.-S.).
E-mail addresses: ioulia@chem.auth.gr (J. Stephanidou-Stephanatou), tsolerid@chem.auth.gr (C.A. Tsoleridis).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.106



Scheme 1. Reaction of 3-formyl-chromones with DMAD and thiazole **3**.

Table 1
Synthesis of thiazolopyridines **4** and benzopyranothiazolopyridines **5**

Entry	R^1	R^2	R^3	Products (%)	
1	H	H	H	**4a** (45)	**5a** (4)[a]
2	Me	H	H	**4b** (5)[b]	**5b** (38)
3	Cl	H	H	**4c** (41)	
4	Cl	Me	H	**4d** (37)	**5d** (5)[a]
5	NO_2	H	H	**4e** (23)	
6	Br	H	Br	**4f** (38)	

[a] As an inseparable mixture with **4**.
[b] As an inseparable mixture with **5**.

indicated the transformation of the chromone to a hydroxybenzoyl moiety. This transformation was identified easily from the splitting pattern of the aromatic protons, resonating as a dd at δ 7.50 (J = 7.6, 1.75 Hz), a ddd at δ 6.91 (J = 7.6, 7.4, 1.1 Hz), a ddd at δ 7.45 (J = 8.25, 7.4, 1.75 Hz) and as a dd at δ 7.03 (J = 8.25, 1.1 Hz)[10] with their carbons resonating at 130.9, 118.6, 134.9 and 118.3 ppm, respectively. Moreover, the hydroxy proton shows COLOC correlations with the quaternary carbon at 161.9 ppm (C-2′), and also with the protonated carbon at 118.3 ppm (C-3′), (Fig. 1). In the

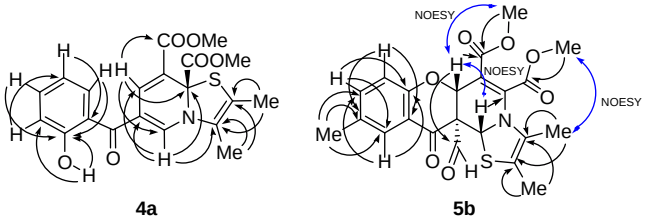


Figure 1. Diagnostic COLOC correlations between protons and carbons (via $^2J_{C-H}$ and $^3J_{C-H}$) in compounds **4a** and **5b**. In **5b**, some important diagnostic NOESY correlations are also included.

^{1}H NMR spectrum, the two carbomethoxy methyl group protons resonated at δ 3.75 and δ 3.84, whereas the two thiazole methyl group protons occurred at δ 2.02 and δ 2.03 showing COLOC correlations with the quaternary carbon signals at 119.1 (C-2) and 125.5 ppm (C-3). In addition, two more protons resonating in the aromatic region were identified, at δ 7.90 and δ 7.98 coupled mutually with J = 1.02 Hz, with their corresponding carbons resonating at 141.6 and 132.1 ppm. These protons had COLOC correlations with a quaternary carbon at 72.8 ppm (C-8a) having very low intensity. The proton at δ 7.98 also correlated with one of the carbomethoxy carbonyls at 165.2 ppm, whereas the proton at δ 7.90 correlated with the quaternary carbon at 109.5 ppm and with the carbon C-7 at 132.1 ppm, indicating the presence of a six-membered ring containing the former thiazole nitrogen. The quaternary carbon at 72.8 ppm, bearing the second carbomethoxy group, is

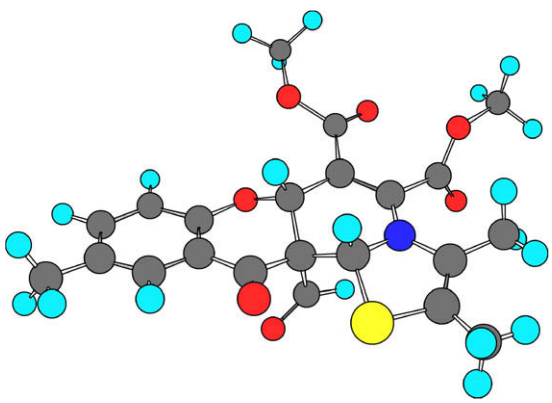
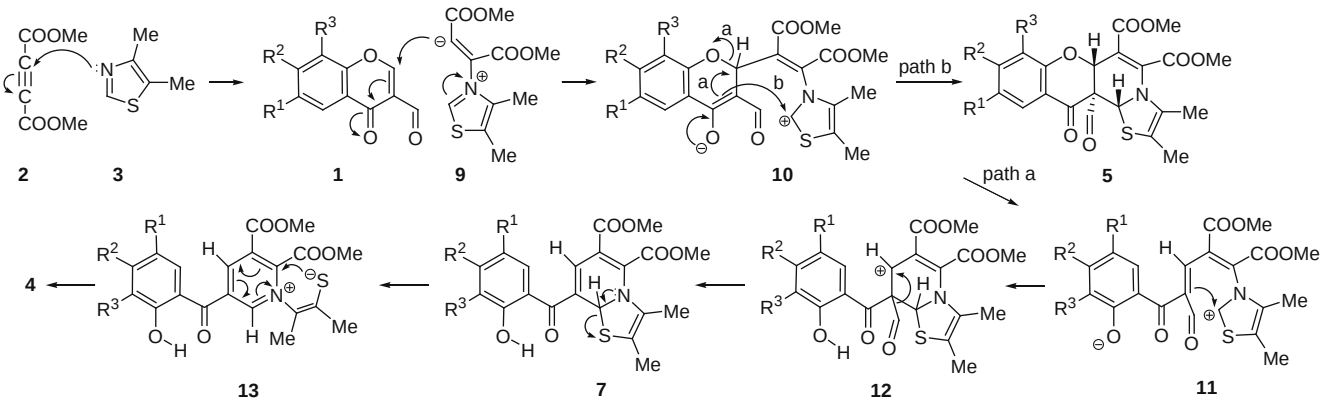


Figure 2. Global lower energy conformation of **5b** calculated by DFT (B3LYP/6-31G(d)).



Scheme 2. A proposed mechanism for the reaction.

also bonded to the sulfur of the thiazole ring, thus indicating that a rearrangement had occurred.

Concerning the structure of **5b,** the presence of a formyl group was detected. The absence of a hydroxyl group in conjunction with the protons resonating at δ 5.60 and δ 5.64, the first correlating with the carbomethoxy carbonyl at δ 165.7 and the second correlating with the quaternary carbon at δ 144.1 (C-5), suggested the presence of a nitrogen-containing six-membered ring. COLOC correlations in conjunction with the NOESY results depicted in Figure 1 confirmed the structure and the *syn*-approximation of protons 6a-H and 12b-H. The global lower energy conformation of **5b**, in accordance with COLOC and NOESY data, calculated by DFT (B3LYP/6-31G(d)) is depicted in Figure 2.

The following mechanistic postulate may be invoked to rationalize the reaction (see Scheme 2). The Huisgen zwitterion **9** formed from the thiazole and DMAD attacks initially the C-2 chromone carbon, instead of the expected aldehyde carbon,[6,11] giving the intermediate **10**, which by chromone ring opening (path a) leads initially to **11** and then by formation of a new six-membered ring to **12**. Deformylation, followed by a 1,5-sigmatropic shift, results in **4** through the formation of the vinyl sulfide zwitterion **13** bearing an aromatic pyridine ring. However, in some derivatives the formation of the cyclohexene ring through path b, before deformylation, most probably stabilizes the system leading stereoselectively to compound **5**.

In conclusion, we have reported the first three-component reaction involving a thiazole-DMAD zwitterion for the synthesis of novel thiazolo- and chromenothiazolopyridines. Moreover, the present work demonstrates the versatility of chromones in one-pot synthetic procedures.

References and notes

1. (a) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125–165; (b) Acheson, R. M.; Elmore, N. F. *Adv. Heterocycl. Chem.* **1978**, *23*, 263–482.
2. Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094–1106.
3. (a) Valenciano, J.; Sánchez-Pavón, E.; Cuadro, A. M.; Vaquero, J. J.; Alvarez-Builla, J. *J. Org. Chem.* **2001**, *66*, 8528–8536; (b) Dombrowski, A.; Nieger, M.; Niecke, E. *Chem. Commun.* **1996**, 1705–1710; (c) Potts, K. T.; Rochanapruk, T.; Coats, S. J.; Hadjiarapoglou, L.; Padwa, A. *J. Org. Chem.* **1993**, *58*, 5040–5042; (d) Potts, K. T.; Dery, M. O. *J. Org. Chem.* **1990**, *55*, 2884–2894; (e) Gotthardt, H.; Riegels, M. *Chem. Ber.* **1988**, *121*, 1143–1146; (f) Ungureanu, I.; Klotz, P.; Shoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958–959; (g) Rigby, J. H. *Synlett* **2000**, 1–12; (h) Tejeda, J.; Reau, R.; Dahan, F.; Bertrand, G. *J. Am. Chem. Soc.* **1993**, *115*, 7880–7881; (i) Facklam, T.; Wagner, O.; Heydt, H.; Regitz, M. *Angew. Chem., Int. Ed.* **1990**, *29*, 314–315.
4. (a) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520–530; (b) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Bhadbhade, M. M.; Gonnade, R. C. *Org. Lett.* **2002**, *4*, 3575–3577; (c) Nair, V.; Sreekanth, A. R.; Biju, A. T.; Rath, N. P. *Tetrahedron Lett.* **2003**, *44*, 729–732.
5. (a) Nair, V.; Devi, B. R.; Varma, R. L. *Tetrahedron Lett.* **2005**, *46*, 5333–5335; (b) Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Ghanzanfarpour-Darzani, M. *Monatsh. Chem.* **2007**, *138*, 677–681; (c) Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2001**, *3*, 3495–3497; (d) Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2002**, *4*, 2807.
6. Adib, M.; Sheibani, I.; Mostofi, M.; Ghanbary, K.; Bizanzadeh, H. R. *Tetrahedron* **2006**, *62*, 3435–3438.
7. (a) Terzidis, M.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Tetrahedron Lett.* **2005**, *46*, 7239–7242; (b) Terzidis, M.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Tetrahedron* **2007**, *63*, 7828–7832.
8. (a) Abbott, P. J.; Acheson, R. M.; Eisner, U.; Watkin, D. J.; Carruthers, J. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 155–156; (b) Maeda, M.; Ito, S.; Kojima, M. *Tetrahedron Lett.* **1976**, *38*, 3463–3466.
9. *General experimental procedure*: DMAD (1.0 equiv) was added to a solution of chromone-3-carboxaldehyde **1a** (1.0 equiv) and 4,5-dimethylthiazole (1.0 equiv) in DME (20 mL) at −10 °C under argon. The system was then allowed to attain room temperature and was stirred for 12 h. Distillation of the solvent in vacuo followed by column chromatography on silica gel using petroleum ether/AcOEt (7:1) as eluent, slowly increasing the polarity up to 3:1 afforded **4a** as a mixture with the minor product **5a**. Crystallization from CH_2Cl_2–Et_2O afforded **4a** as a pure compound. All attempts to obtain pure **5a** by preparative TLC were unsuccessful because of decomposition. NMR spectra were recorded at room temperature on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent.
*6-(2′-hydroxybenzoyl)-8,8a-dimethoxycarbonyl-2,3-dimethyl-8aH-[1,3]thiazolo-[3,2-a]pyridine (**4a**).* Orange crystals; mp 208–209 °C (CH_2Cl_2–Et_2O). IR (Nujol) ν_{max}: 3458, 1738, 1698 cm^{-1}. ^{1}H NMR: 2.02 (s, 3H, 2-CH_3), 2.03 (s, 3H, 3-CH_3), 3.75 (s, 3H, 8a-OCH_3), 3.84 (s, 3H, 8-OCH_3), 6.91 (ddd, J = 7.6, 7.4, 1.1 Hz, 1H, 5′-H), 7.03 (dd, J = 8.25, 1.1 Hz, 1H, 3′-H), 7.45 (ddd, J = 8.25, 7.4, 1.75 Hz, 1H, 4′-H), 7.50 (dd, J = 7.6, 1.75 Hz, 1H, 6′-H), 7.90 (d, J = 1.02 Hz, 1H, 5-H), 7.98 (d, J = 1.02 Hz, 1H, 7-H), 11.63 (s, 1H, OH). ^{13}C NMR: 11.2 (3-CH_3), 12.7 (2-CH_3), 52.1 (8-OCH_3), 53.7 (8a-OCH_3), 72.8 (C-8a), 107.5 (C-8), 109.5 (C-6), 118.3 (C-3′), 118.6 (C-5′), 119.1 (C-2), 120.1 (C-1′), 125.5 (C-3), 130.9 (C-6′), 132.1 (C-7), 134.9 (C-4′), 141.6 (C-5), 161.9 (C-2′), 165.2 (8-C=O), 169.3 (8a-C=O), 192.8 (6-C=O). MS (LCMS) *m/z* (%) 402 (100, M$^+$+1). Anal. Calcd for $C_{20}H_{19}NO_6S$ (401.43): C, 59.84; H, 4.77, N, 3.49. Found: C, 59.93; H, 4.83; N, 3.40.
*12a-formyl-5,6-dimethoxycarbonyl-2,3,10-trimethyl-12-oxo-12a,12b-dihydro-6aH, 12H-chromeno[3,2-c][1,3]thiazolo[3,2-a]pyridine (**5b**).* Orange crystals; mp 189–192 °C (CH_2Cl_2–Et_2O). IR (Nujol) ν_{max}: 1735, 1708, 1662 cm^{-1}. ^{1}H NMR: 1.83 (q, J = 1.0 Hz, 3H, 3-CH_3), 1.93 (q, J = 1.0 Hz, 3H, 2-CH_3), 2.32 (s, 3H, 10-CH_3), 3.78 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 5-OCH_3), 5.60 (s, 1H, 6a-H), 5.64 (s, 1H, 12b-H), 6.92 (d, J = 8.5 Hz, 1H, 8-H), 7.36 (dd, J = 8.5, 2.2 Hz, 1H, 9-H), 7.67 (d, J = 2.2 Hz, 1H, 11-H), 10.16 (s, 1H, 12a-CHO). ^{13}C NMR: 11.9 (3-CH_3), 13.6 (2-CH_3), 20.5 (10-CH_3), 52.0 (6-OCH_3), 53.2 (5-OCH_3), 58.7 (C-12a), 63.0 (C-6a), 71.1 (C-12b), 114.2 (C-2), 117.6 (C-6), 118.3 (C-8), 119.8 (C-11a), 126.8 (C-11), 127.4 (C-3), 132.1 (C-10), 138.5 (C-9), 144.1 (C-5), 159.1 (C-7a), 164.2 (5-C=O), 165.7 (6-C=O), 187.4 (C-12), 196.8 (12a-C=O). MS (LCMS) *m/z* (%) 444 (100, M$^+$+1), 416 (91). Anal. Calcd for $C_{22}H_{21}NO_7S$ (443.47): C, 59.58; H, 4.77, N, 3.16. Found: C, 59.43; H, 4.68; N, 3.22.
10. Simulated with SpinWorks simulation program, version 2.5, available from ftp://davinci.chem.umanitoba.ca.
11. (a) Yavari, I.; Sabbaghan, M.; Hossaini, Z. *Synlett* **2006**, 2501–2503; (b) Nair, V.; Devipriya, S.; Eringathodi, S. *Tetrahedron Lett.* **2007**, *48*, 3667–3670.