Tetrahedron 66 (2010) 3651–3654

Contents lists available at ScienceDirect

Tetrahedron

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

Reaction of dialkyl 2-butynoate with aniline and formaldehyde: revision of the structure of the product

A. Srikrishna *, M. Sridharan, K.R. Prasad

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

ARTICLE INFO

Article history:
Received 3 March 2010
Received in revised form 20 March 2010
Accepted 23 March 2010
Available online 27 March 2010

Keywords:
Domino reactions
Dialkyl 2-butynoates
1,3-Dioxazines
Tetrahydropyrimidines
3-oxo-2-Pyrrolidinones
Structure revision
Multi-component reaction

ABSTRACT

Dimethyl 3-(aryl)-3,6-dihydro-2*H*-1,3-oxazine-4,5-dicarboxylate structure assigned for the products obtained in the Bronsted acid catalyzed reaction of dimethyl but-2-ynoates with anilines and an excess of formaldehyde in methanol has been revised to methyl 1-(aryl)-3-(methoxymethyl)-4,5-dioxopyrrolidine-3-carboxylate.

1. Introduction

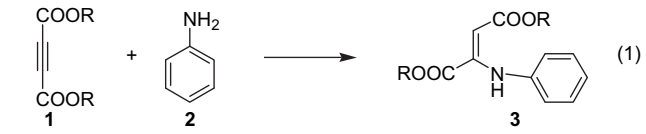
Domino reactions including multi-component reactions have become very popular among synthetic chemists as a powerful tool to accomplish molecular complexity and diversity from readily accessible starting materials in one single operation.[1] Transition-metal-catalyzed multi-component reactions have attracted considerable attention due to the fact that complicated organic molecules including lead compounds for drugs can be easily prepared from simple compounds in one reaction sequence. The development of new multi-component reactions that allow assembly of polysubstituted heterocycles in a regioselective manner is in high demand, particularly, those avoiding transition metal catalysts and/or harsh conditions. In this context, three and four-component domino reactions involving dialkyl 2-butynoates with amines and aldehydes have generated useful heterocyclic systems, such as dihydropyrimidines and tri and tetrasubstituted pyrrolidinones. However, analogous extrapolation of a set of reactions, e.g., formation of azaheterocycles, to other set, e.g., formation of oxaheterocycles, without proper analysis of the spectral data may lead to wrong structures, as the reactions may take different mechanistic pathway. Herein, we report the structure revision of the dihydro-1,3-oxazines reported to be generated in the Bronsted acid catalyzed reaction of dialkyl 2-butynoates with one equivalent of aniline and an excess of formaldehyde.

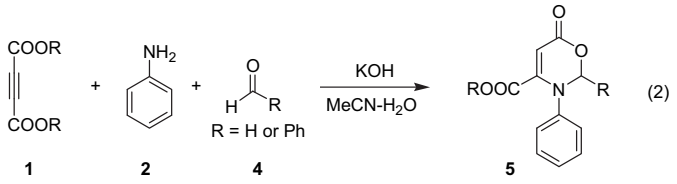
2. Results and discussion

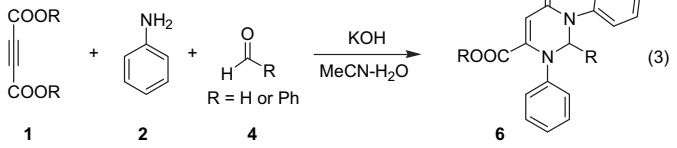
Reaction of dialkyl 2-butynoates with amines and aldehydes generated a number of products depending upon the ratio of the reagents involved and also the catalysts and conditions employed including solvents.[2–6] For example, reaction of dialkyl butynoate **1** with one equivalent of aniline **2** (or a primary or secondary amine) in the absence of formaldehyde generates simple Michael addition product **3** (Eq. 1). Potassium hydroxide catalyzed reaction of **1** with one equivalent of aniline (or amine) and one equivalent of an aldehyde **4** in aqueous acetonitrile leads to the formation of 1,3-oxazin-6-ones **5** (Eq. 2), whereas with two equivalents of aniline forms the 1,3-pyrimidin-4-ones **6** (Eq. 3). Acetic acid catalyzed reaction of **1** with two equivalents aniline **2** and three equivalents of formaldehyde generates the 1,3-diaryl tetrahydropyrimidinedicarboxylate **7** (Eq. 4). Unsymmetrically substituted tetrahydropyrimidines **8** and **9** could also be generated by employing one equivalent of aniline **2** and one equivalent of an amine, e.g., benzylamine, by altering the sequence of addition of amines in refluxing DMF (Eqs. 5 and 6).

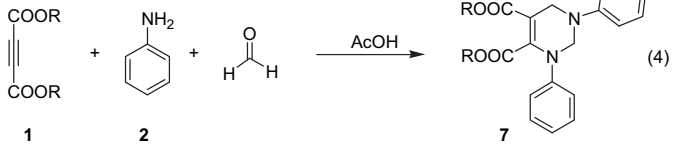
* Corresponding author. Tel.: +91 80 22932215; fax: +91 80 23600529; e-mail address: ask@orgchem.iisc.ernet.in (A. Srikrishna).

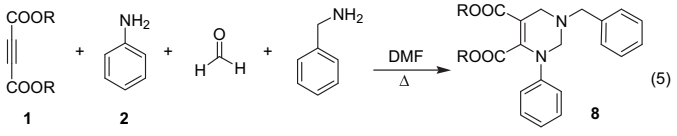
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.084

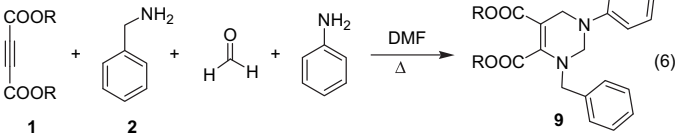












Recently, as an extrapolation of these studies, Jiang et al. reported[7] an efficient synthesis (70–85% yield) of a number of 3,6-dihydro-(2*H*)-1,3-oxazinedicarboxylates **10** by employing one equivalent of the diester **1**, one equivalent of an aniline **2** and an excess of formaldehyde in methanol in the presence of a catalytic amount of hydrochloric acid. However, perusal of the reported[7] spectral data (cf. Table 1) for the compounds **10** revealed several anomalies, in particular, in comparison with their aza-analogues, the corresponding tetrahydropyrimidines **7** (cf. Eq. 4).

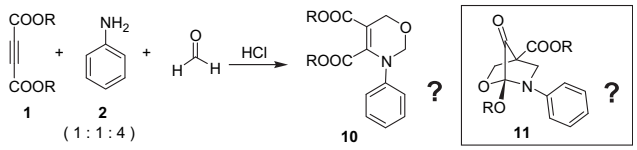


Table 1
Spectral data reported[7] for the compound **10** (R=Me)

IR (KBr) ν_{max}/cm^{-1}	^1H NMR (400 MHz, $CDCl_3$) δ ppm	^{13}C NMR (100 MHz, $CDCl_3$) δ ppm
3395, 3045,	7.86 (2H, d, *J*=8 Hz)	193.2,
2858,	7.47 (2H, d, *J*=8 Hz)	166.4, 156.2,
1769, 1700,	7.31 (1H, t, *J*=7.2 Hz)	
1457, 1091,	4.52 (1H, d, *J*=10.8 Hz)	138.3, 129.3,
753	4.27 (1H, d, *J*=10 Hz)	127.1, 119.5,
	4.00 (1H, d, *J*=9.2 Hz)	
	3.89 (1H, d, *J*=9.2 Hz)	72.8, 59.6, 55.1,
	3.77 (3H, s) and 3.32 (3H, s)	53.7, 48.9

For example, all the compounds exhibited a carbonyl absorption band at around 1770 cm^{-1} (absent in **7**) in the IR spectra, which is not accountable for the structure **10**. The absorption band at 1770 cm^{-1} is generally due to either a strained ketone (e.g., 7-ketonorbornane) or a butyrolactone or an aryl ester or a pyruvic acid derivative, and cannot be due to a conjugated ester as in **10**. In the ^1H NMR spectra, two protons of the aromatic moiety resonated at δ ~7.8 ppm, in contrast to those appeared at δ 7.23 in the corresponding pyrimidine **7**. The C-2 methylene in **10** resonated upfield at δ ~4.5 and 4.3 when compared to the C-2 methylene in the dihydropyrimidines **7** (δ ~4.8 ppm), instead of shifting to down field (as it is now attached to one oxygen and one nitrogen in **10**, instead of two nitrogens as in **7**). Most strikingly, ^{13}C NMR spectra contained a signal at δ ~193 ppm (resonance most probably due to a ketone carbon) and an extra aliphatic quaternary carbon signal at δ ~55 ppm for the compounds **10**. The most down field aliphatic methylene carbon in **10** was resonated at δ ~72 ppm (δ ~69 ppm in **7** for the C-2 carbon), whereas an aliphatic carbon attached to oxygen and nitrogen (C-2 in **10**) is expected to resonate in the range of ~80–90 ppm. These spectral data clearly established that the structure **10** proposed for the product is wrong.

Based on the spectroscopic data, initially, an alternate structure **11** containing a strained ketone (similar to 7-ketonorbornane) and a quaternary aliphatic carbon in addition to an orthoester type carbon (expected to resonate around 120–130 ppm) was considered as a possibility, since it satisfies all the spectral data. However, it is very unlikely that such a strained orthoester will be able to exist under the reaction conditions (presence of aqueous HCl). In order to unambiguously establish the structure of the product, the reaction was reinvestigated. Chloroaniline **2a** was opted as the aniline component, and the reaction was performed employing the conditions described[7] by Jiang et al. Thus, reaction of one equivalent of dimethyl acetylenedicarboxylate **1a** with one equivalent of *p*-chloroaniline **2a** in the presence of a catalytic amount of hydrochloric acid in methanol, followed by addition of five equivalents of aqueous formaldehyde, under unoptimized conditions, furnished a mixture of two compounds, which were separated by column chromatography on silica gel. The less polar compound was identified as the tetrahydropyrimidine diester **7a** by comparing the spectral data with that reported in the literature.[6] The polar compound **12** exhibited spectral data (IR, ^1H and ^{13}C NMR) identical to that reported[7] by Jiang et al. for the 1,4-oxazine diester **10a**.

As mentioned earlier, based on the spectral data a logical structure could not be assigned. In order to unambiguously establish the structure of the product, a single crystal X-ray diffraction

analysis was carried out. Thus, recrystallization of the compound **12** from a mixture of methylene chloride and hexane, followed by single crystal X-ray diffraction analysis (an ORTEP diagram is depicted in Fig 1) revealed the structure of the product as methyl 1-(4-chlorophenyl)-3-(methoxymethyl)-4,5-dioxopyrrolidine-3-carboxylate **12**. All the spectral data (IR, ^{1}H and ^{13}C NMR) is consistent with the dioxopyrrolidine[8] structure **12**, such as the presence of ketone of pyruvate in a five membered ring system (IR and ^{13}C NMR), two isolated methylenes (one attached to oxygen and other attached to nitrogen), a quaternary aliphatic carbon (C-3), shift in the aromatic signals due to the acyl group on nitrogen.

A tentative mechanism for the formation of the ester **12**, considering that the product is formed when only one equivalent of aniline is employed, is depicted in Scheme 1. Initial Michael addition of aniline **2** to the diester **1** generates the enamine **3**. An aza ene type (or Prins type) addition of the enamine **3** to the oxonium ion **13**, derived from formaldehyde and methanol, followed by isomerisation of the imine to enamine generates the new enamine **14**. Coupling of the nitrogen in **14** with one more equivalent of **13** produces **15**, which on elimination of methanol yields the iminium ion **16**. Michael addition of water to the conjugated ester in **16** followed by cyclisation leads to the azetidine **17**. Generation of the

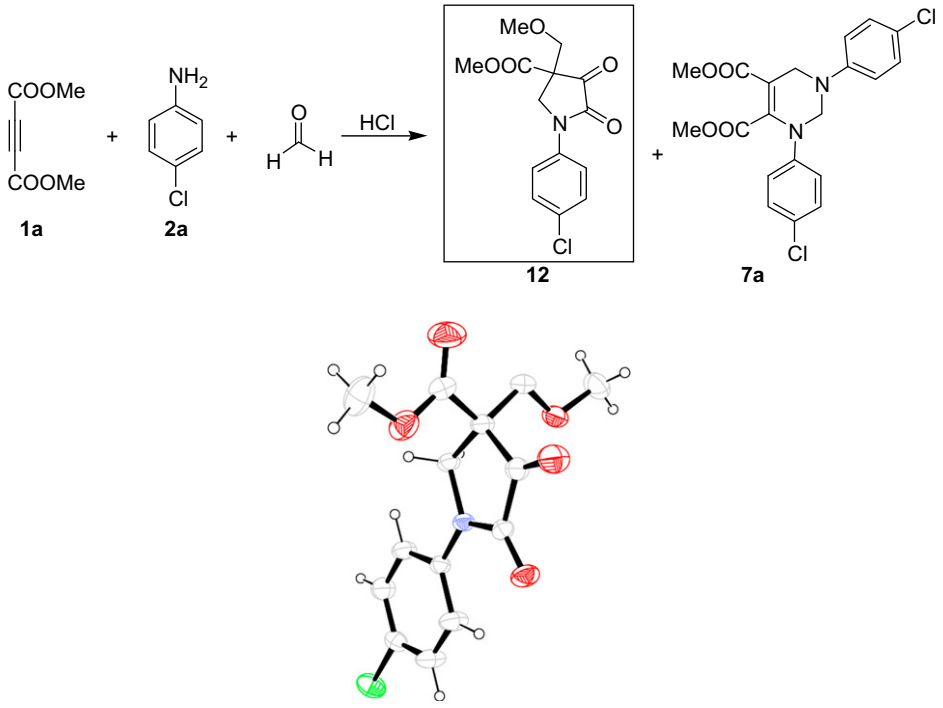
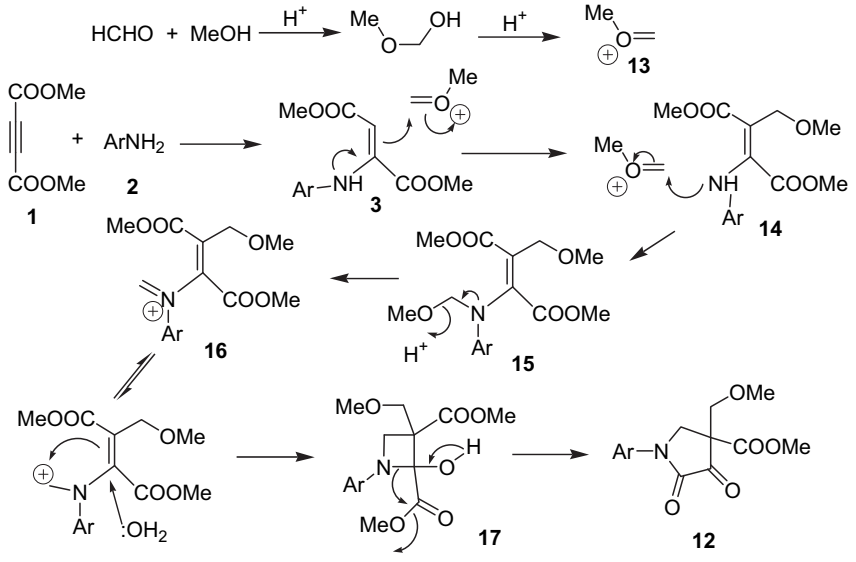


Figure 1. ORTEP diagram of molecule B drawn at 30% probability displacement ellipsoids (the minor occupied site (35%) of the disordered carbonyl oxygen is omitted for clarity; also the hydrogen positions on the disordered carbon atom are not refined).



Scheme 1.

ketone via cleavage of the C–N bond in **17** followed by intramolecular lactamisation furnishes the product **12**.

3. Conclusions and summary

The 1,3-oxazine based structure **10** assigned for the product obtained in the Bronsted acid catalyzed reaction of dialkyl but-2-ynoates with anilines and an excess of formaldehyde in methanol was deduced to be wrong. The new structure **12** based on 2,3-dioxopyrrolidine-3-carboxylate was established through single crystal X-ray diffraction analysis of the product obtained. A tentative mechanism is proposed for the formation of **12** via the Michael addition product **3**.

4. Experimental section

4.1. General

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Brucker AMX 400 spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. Elemental analyses were carried out using Carlo Erba 1106 CHN analyzer at the Department of Organic Chemistry, Indian Institute of Science, Bangalore.

*4.1.1. Dimethyl 1,3-bis(4-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate (**7a**) and methyl 1-(4-chlorophenyl)-3-(methoxymethyl)-4,5-dioxopyrrolidine-3-carboxylate (**12**).* To a magnetically stirred solution of *p*-chloroaniline **2a** (127 mg, 1 mmol) in methanol (3 mL) was added dimethyl acetylenedicarboxylate **1a** (142 mg, 1 mmol). The reaction mixture was stirred for 10 min at rt. To the reaction mixture 0.01 M HCl (2 mL), followed by formaldehyde (39% aqueous solution, 0.4 mL, 5 mmol) were added and stirred for 30 min. The solvent was removed under reduced pressure, water (10 mL) was then added to the reaction mixture and extracted with ether (3×5 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as eluent first furnished dimethyl 1,3-bis(4-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **7a** (110 mg, 52%) as white solid. Mp 127–129 °C; [Found: C, 57.04; H, 4.50; N, 6.93. $C_{20}H_{18}ClN_2O_4$ requires C, 57.02; H, 4.31; N, 6.65%]; R_f (30% EtOAc/hexane) 0.5; IR (KBr): ν_{max}/cm^{-1} 2951, 1743, 1703, 1588, 1495, 1435, 1260, 1232, 1214, 1115, 1094, 832; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, d, J=8.7 Hz), 7.18 (2H, d, J=8.7 Hz), 6.90 (2H, d, J=8.7 Hz), 6.80 (2H, d, J=8.7 Hz), 4.84 (2H, s, H-2), 4.21 (2H, s, H-6), 3.74 (3H, s, OCH_3), 3.60 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C, OC=O), 164.2 (C, OC=O), 146.6 (C), 145.9 (C), 142.0 (C), 132.1 (C), 129.5 (2C, CH), 129.2 (2C, CH), 126.2 (C), 126.0 (2C, CH), 119.1 (2C, CH), 101.4 (C, C-5), 68.9 (CH_2, C-2), 52.7 (CH_3), 51.7 (CH_3), 47.4 (CH_2, C-6). Further elution of the column with ethyl acetate/hexane (1:4) furnished methyl 1-(4-chlorophenyl)-3-(methoxymethyl)-4,5-dioxopyrrolidine-3-carboxylate **12** (105 mg, 34%) as a white solid, which was recrystallised from a mixture of methylene chloride and hexane. Mp 164–166 °C; [Found: C, 53.57; H, 4.66; N, 4.83. $C_{14}H_{14}ClNO_5$ requires C, 53.94; H, 4.53; N, 4.49%]; R_f (30% EtOAc/hexane) 0.4; IR (KBr): ν_{max}/cm^{-1} 3112, 2955, 1776, 1739, 1714, 1495, 1455, 1435, 1309, 1330, 1232, 1100, 1002, 825, 734; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 and 7.44 (4H, 2×d, J=8.9 Hz, Ar–H), 4.51 and 4.24 (2H, 2×d, J=10.4 Hz, CH_2OMe), 4.01 and 3.89 (2H, 2×d, J=9.0 Hz, H-2), 3.78 (3H, s, $COOCH_3$), 3.32 (3H, s, CH_2OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7 (C, C=O), 166.2 (C, OC=O), 156.1 (C, NC=O), 136.9 (C), 132.4 (C), 129.4 (2C, CH), 120.6 (2C, CH), 72.8 (CH_2, CH_2OMe), 59.6 (CH_3, OCH_3), 55.0 (C, C-3), 53.7 (CH_3, OCH_3), 48.8 (CH_2, C-2).

Crystal data for the compound **12**: X-ray data were collected at 291 K on a SMART CCD-BRUKER diffractometer with graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods (SIR 92). Refinement was by full-matrix least-squares procedures on F2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. Mol. For. $C_{14}H_{14}ClNO_5$; MW=311.71; colourless; Crystal system: Triclinic; Space group *P*-1; cell parameters, a=6.5900(2) Å, b=7.8571(3) Å, c=15.5749(5) Å; α 78.882(2), β 88.220(2), γ 65.933(2), V=721.50(4) Å^3, Z=2, D_c=1.435 g cm^{-3}, F(000)=324, μ=0.285 mm^{-1}. Total number of l.s. parameters=203, $R1$=0.0508 for 2235 $F_0>2\sigma(F_0)$ and 0.0921 for all 3761 data. $wR2$=0.1285, GOF=1.207, restrained GOF=1.207 for all data. An ORTEP diagram is depicted in Figure 1. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 767892).

Acknowledgements

We thank Ms. S. Brinda, CCD Facility, Indian Institute of Science for the X-ray diffraction analysis, and Council of Scientific and Industrial Research, New Delhi for the award of a research associate position to MS.

References and notes

1. (a) *Multi-Component Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005; (b) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, 2006.
2. Zhang, M.; Jiang, H.-F.; Wang, A. Z. *Synlett* **2007**, 3214.
3. Zhang, M.; Jiang, H.-F. J.; Liu, H. L.; Zhu, Q. H. *Org. Lett.* **2007**, *9*, 4111.
4. Cao, H.; Wang, X. J.; Jiang, H.-F.; Zhu, Q. H.; Zhang, M.; Liu, H. Y. *Chem.—Eur. J.* **2008**, *14*, 11623.
5. Zhu, Q.; Jiang, H.-F.; Li, J.; Liu, S.; Xia, C.; Zhang, M. *J. Comb. Chem.* **2009**, *11*, 685.
6. Zhu, Q.; Jiang, H.-F.; Li, J.; Zhang, M.; Wang, X.; Qi, W. *Tetrahedron* **2009**, *65*, 4604.
7. Cao, H.; Jiang, H.-F.; Qi, C.-R.; Yao, W.-J.; Chen, H.-J. *Tetrahedron Lett.* **2009**, *50*, 1209.
8. Mohri, K.; Yokoyama, K.; Komiya, H.; Watanabe, Y.; Yoshida, Y.; Isobe, K.; Tsuda, Y. *Chem. Pharm. Bull.* **2003**, *51*, 502.