

3-(4-IODOMETHYL-2-OXO-1-AZETIDINYL)PROPYNOIC ACID *t*-BUTYL ESTER: A NEW  $\beta$ -LACTAM  
DERIVATIVE. SYNTHESIS OF AN YNAMIDE BY REACTION OF 4-IODOMETHYLAZETIDIN-2-ONE  
WITH THE *t*-BUTYL ESTER OF PROPIOLIC ACID IN THE PRESENCE OF COPPER(I)

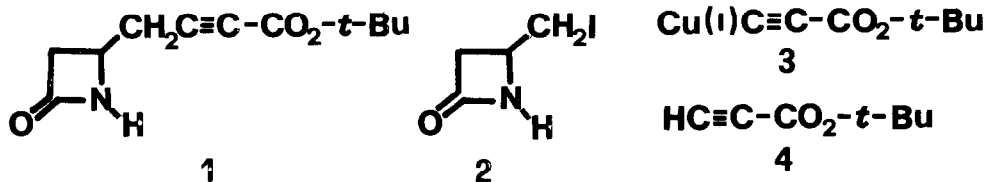
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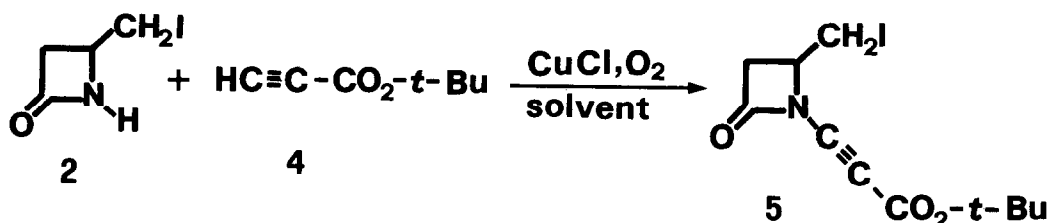
*SUMMARY: The reaction of 4-iodomethylazetidin-2-one (2) with the t-butyl ester of propiolic acid (4) in the presence both of equimolar amounts of copper(I) and oxygen results unexpectedly in the formation of the  $\beta$ -lactam ynamide 5. Its structure was suggested by spectroscopic data and confirmed by single-crystal X-ray analysis.*

In a program aimed at developing new methods to build up bicyclic  $\beta$ -lactam systems, we were looking for a novel and more suitable route to the known acetylenic esters of type 1.<sup>1</sup> An attractive way to these compounds appeared to be the displacement of the iodine of 4-iodomethylazetidin-2-one (2), which can easily be obtained from allyl iodide and chlorosulphonyl isocyanate,<sup>2</sup> with the proper alkynyl substituent. The iodine of type 2 derivatives is reactive and can be substituted under appropriate conditions.<sup>2,3</sup>



In this connection we were attempting to make compound 2 react with the copper(I)-acetylenide (3)<sup>4</sup> of the *t*-butyl ester of propiolic acid (4). When a

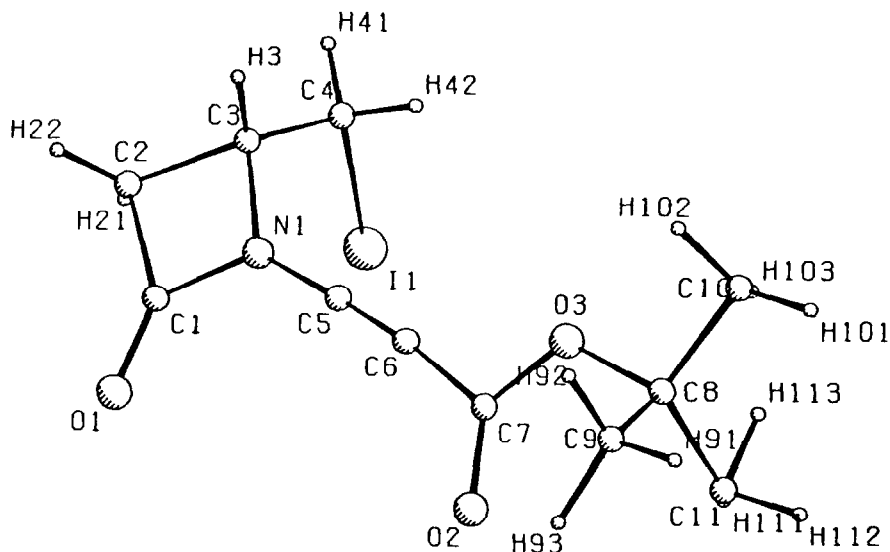
solution of **2** in hexamethylphosphoramide (HMPA) was treated with the copper(I)-acetylenide (**3**) at room temperature for 40 minutes, a crude product was obtained, which by flash chromatography afforded a 10% yield of a solid compound **5**, m.p. 78-80° C (CHCl<sub>3</sub>-hexane). No trace of the desired product of type **1** was found. Compound **5** was also obtained when the reaction of **2** in HMPA was carried out with the propiolic ester **4**, followed by an equimolar addition of CuCl. The yields of **5** were improved by up to 40% both when the reactions were carried out at a lower temperature (0° C), and when oxygen was bubbled into the reaction mixture. The nature of the solvent was found not to be essential; compound **5** was also obtained when the reactions were carried out in dimethylformamide (DMF) or MeCN. The use of less than equimolar amounts of Cu(I) derivatives reduced the yields of **5** proportionally. However when the reactions were performed either without Cu(I) derivatives or under nitrogen, no trace of **5** was found. Attempts to make azetidin-2-ones different from **2** (i.e. 4-acetoxy-, 4-phenylsulphonyl-, and 4-allyl-azetidin-2-one) react with the propiolic ester **4**, under the conditions used to obtain **5** from **2**, did not afford any trace of ynamides of type **5**.



Elemental analysis, IR data,<sup>5</sup> and <sup>1</sup>H-<sup>6</sup> and <sup>13</sup>C-NMR<sup>7</sup> spectra suggested for **5** the structure shown. However, because of the unusual type of structure hypothesized for **5**, we thought it worth while to confirm it unequivocally by X-ray crystallographic analysis of a single crystal of **5**.<sup>8</sup> A projection of the molecule along the (010) axis is shown in Figure.<sup>12</sup>

Ynamines are a well-known class of organic compounds.<sup>17,18</sup> On the contrary ynamides, which may be considered to be somewhat structurally related to ynamines, to the best of our knowledge have not been reported so far. Among the syntheses of ynamines,<sup>17,18</sup> one implies the reaction of terminal alkynes with secondary amines in the presence of copper(II) acetate and oxygen.<sup>18</sup> This synthesis could appear to be analogous to the reaction under investigation leading to **5**. It may be pointed out, however, that the synthesis which gives ynamines can be accomplished using just catalytic amounts of copper(II) salt, and yields are improved when the reactions are carried out in the presence of a reducing agent (e.g. hydrazine). On the contrary, our reaction needed stoichiometric amounts of copper(I) derivatives. The use of less than equimolar

amounts of Cu(I) derivatives, also in the presence of a reducing agent such as hydrazine, reduces the yield of **5** proportionally. The formation of **5** does not occur at all when copper(II) salts (either acetate or chloride) are used.



The formation of the ynamide **5** is somewhat surprising. Undoubtedly the reaction of the 4-iodomethylazetidion-2-one (**2**) with CuCl and the propiolic ester (**4**) which affords **5** can not be ascribed to any kind of simple substitution. It can be formally considered as an oxidation reaction. However this reaction is difficult to visualize. It is worth pointing out however that the presence either of a free-radical inhibitor (hydroquinone) other than oxygen or a free-radical source (azobisisobutyronitrile) in the reaction mixtures does not affect in any way the reaction of **2** and **4** which gives **5**.

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#### References and Notes

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4. The copper(I)-acetylenide **3** was prepared by treating dropwise at r.t. a stirred solution of **4** (1.0 g) in 1:1 EtOH-H<sub>2</sub>O (25 ml) with a solution of CuCl (1.96 g) in 20% aqueous NH<sub>4</sub>OH (25 ml). After 1 h the solution was diluted with H<sub>2</sub>O, filtered, and the solid obtained was washed (aqueous 20% NH<sub>4</sub>OH, H<sub>2</sub>O, 1:1 EtOH-H<sub>2</sub>O, and Et<sub>2</sub>O) and dried under vacuum to yield **3** (0.91 g): IR (nujol)  $\nu_{\max}$  1925 (C≡C) and 1674 cm<sup>-1</sup> (ester C=O).

5. IR:  $\nu_{\max}$  (nujol) 2210 (C≡C), 1782 ( $\beta$ -lactam C=O), and 1685  $\text{cm}^{-1}$  (ester C=O);  $\nu_{\max}$  (CHBr<sub>3</sub>) 1794  $\text{cm}^{-1}$  ( $\beta$ -lactam C=O).
6. <sup>1</sup>H NMR (CDCl<sub>3</sub>). Refining of the spectral parameters of the ABCDM portion of **5**, obtained at 80 MHz, was carried out by a LEQUOR computer program:  $\delta$  2.86 (1H, dd, J=3.32 and -16.30 Hz, 3-H), 3.22 (1H, dd, J=5.78 and -16.30 Hz, 3H), 3.32 (1H, dd, J=8.37 and -10.82 Hz, HCHI), 3.60 (1H, dd, J=3.53 and -10.82 Hz, HCHI), and 4.09 ppm (1H, m, J=8.37, 5.78, 3.53, and 3.32 Hz, CHN).
7. <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  4.05 (CH<sub>2</sub>I), 27.92 (CH<sub>3</sub>), 45.26 (CH<sub>2</sub>), 55.21 (CHN), 67.83 and 72.22 (C≡C), 152.60 and 164.20 ppm (two C=O groups).
8. Crystal Data. C<sub>11</sub>H<sub>14</sub>NO<sub>3</sub>I, M=335.14, triclinic, P $\bar{1}$ , a=11.263(2), b=11.052(2), c=5.740(1) Å,  $\alpha$ =104.8(2),  $\beta$ =92.99(2),  $\gamma$ =79.06(2)°, from diffractometer measurement ( $\lambda$ =0.71069 Å), U=678.18(22) Å<sup>3</sup>,  $d_c$ =1.641 g.cm<sup>-3</sup>, Z=2, F(000)=328,  $\mu(\text{MoK}\alpha)$ =23.3 cm<sup>-1</sup>. The data were collected with a PW 1100 Philips automatic diffractometer using MoK $\alpha$  radiation; absorption correction was given following North, Phillips and Mathews.<sup>9</sup> The structure was solved by direct methods<sup>10</sup> and refined with full-matrix least-squares<sup>10</sup> to an R value of 3.63% [ $R_w$ =3.69%;  $w=1.35/\sigma(F)^2+0.0002F^2$ ] for 2123 observed reflections. Geometric calculations were performed with PARST program.<sup>11</sup>
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12. From the crystallographic data it is found that the four-membered ring in **5** shows a trend similar to those found in some cephem<sup>13</sup> and penam<sup>14</sup> derivatives, the angle between the N1-C1-C3 and C1-C2-C3 planes being 6.6(4)°; the C5-C6 bond of 1.191(9) Å is very near the value found for the solid acetylene;<sup>15</sup> the N1-C5-C6-C7 side chain is practically linear, as indicated by the values of the N1-C5-C6 and C5-C6-C7 angles [176.7(6) and 173.0(7)°, respectively]; the C-I bond is in the range of the paraffinic values shown in Tables of Interatomic Distances,<sup>16</sup> and one of the C-C distances of the *t*-butyl group is significantly longer than the other ones.  
Tables of fractional atomic coordinates, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre.
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