REACTIONS OF ISOCYANATES WITH ETHYL 2-AMINO-1-CYCLOPENTENE-1-CARBOXYLATE

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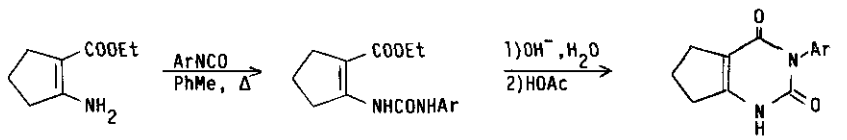
Abstract - Aromatic isocyanates react with ethyl 2-amino-1-cyclopentene-1-carboxylate to yield the corresponding ureas, which cyclize by base to 3-substituted 6,7-dihydro-1H-cyclopentapyrimidine-2,4(3H,5H)-diones.

As part of a study of cyclization reactions of 2-aminoesters and 2-aminonitriles with isocyanates,[2-4] we investigated briefly such reactions of ethyl 2-amino-1-cyclopentene-1-carboxylate (1). Only isolated examples of reactions of 1 with isocyanates have been reported in the literature.[5-7] We have found that when equimolar quantities of 1 and an aromatic isocyanate are refluxed in toluene for 16-20 hours, the corresponding urea (2) is obtained in 45-78% yield.



1 2 3

Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4

In earlier work, it was established that analogous ureas derived from methyl 2-aminobenzoate cyclize to 3-substituted 2,4(1H,3H)-quinazolinediones by the action of dilute acid,[8-11] or base,[4] but to N-substituted 2-amino-4H,-3,1-benzoxazin-4-ones by treatment with concentrated sulfuric acid.[4] In the present case, ureas 2 have been found to resist cyclization upon refluxing with hydrochloric acid in ethanol, but to be converted into the expected 3-aryl-6,7-dihydro-1H-cyclopentapyrimidine-2,4(3H,5H)-diones (3) in 61-72% yield by treatment with hot, dilute alkali. Earlier preparations of compounds 3 were generally based on the acid catalyzed reactions of ethyl 2-oxocyclopentane-1-carboxylate with ureas.[12,13]

The room temperature treatment of ureas 2 with concentrated sulfuric acid failed to yield the anticipated[4] 2-(N-arylamino)-6,7-dihydrocyclopent-4H-3,1-oxazin-4(5H)-ones. Whereas relatively brief reaction periods led to the recovery of starting material, more prolonged treatment yielded only water soluble products, which were not investigated.

EXPERIMENTAL

Melting points were determined in capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared and ^{1}H-nmr spectra were recorded on a Perkin-Elmer 337 and a Varian EM 360 spectrometer, respectively, as indicated in the Tables.

Ethyl 2-[[(Arylamino)carbonyl]amino]-1-cyclopentene-1-carboxylates (2). After a mixture of 0.020 mole of ethyl 2-amino-1-cyclopentene-1-carboxylate (1), 20 ml of toluene, and 0.020 mole of an isocyanate had been refluxed overnight (16-20 hours), the solvent was removed by distillation under reduced pressure to yield the corresponding 2 (Table 1).

3-Aryl-6,7-dihydro-1H-cyclopentapyrimidine-2,4-(3H,5H)-diones (3). A mixture of 1.0 g of a urea 2 and 20 ml of 5% aqueous sodium hydroxide was heated on a steambath to form a solution, which was filtered from a small amount of insoluble material, cooled, and acidified with acetic acid to afford the corresponding 3 (Table 2).

Table 1. Ethyl 2-[[(Arylamino)carbonyl]amino]-1-cyclopentene-1-carboxylates (2)[a]

Ar	Yield(%)	Mp(°C)	IR(cm^{-1})[b]	^{1}H-NMR(ppm)[c]
Ph	45	126-128[d,e]	3250(N-H),1660(C=O),1620(C=C)	1.2(t,3,CH_3),1.8(m,2,4-CH_2),2.4 (m,2,5-CH_2),3.1(m,2,3-CH_2),4.2 (q,2,CH_2CH_3),6.9-7.6(m,5,ArH), 9.8(s,1,NH),10.0(s,1,NH)
2-MeC_6H_4	50	141-142[f]	3280(N-H),1670(C=O),1620(C=C)	1.3(t,3,CH_2CH_3),1.9(m,2,4-CH_2), 2.3(s,3,CH_3),2.5(m,2,5-CH_2),3.2 (m,2,3-CH_2),4.2(q,2,CH_2CH_3), 7.6-7.9(m,4,ArH),9.3(s,1,NH), 9.9(s,1,NH)
3-MeC_6H_4	66	151-153[f]	3250(N-H),1670(C=O),1630(C=C)	1.2(t,3,CH_2CH_3),1.8(m,2,4-CH_2), 2.3(s,3,CH_3),2.4(m,2,5-CH_2),3.1 (m,2,3-CH_2),4.2(q,2,CH_2CH_3), 6.8-7.4(m,4,ArH),9.8(s,1,NH), 9.9(s,1,NH)
4-MeC_6H_4	83	124.5-126[g]	3460,3280(N-H),1680,1650(C=O), 1620(C=C)	1.2(t,3,CH_2CH_3),1.9(m,2,4-CH_2), 2.2(s,3,CH_3),2.4(m,2,5-CH_2),3.1 (m,2,3-CH_2),4.1(q,2,CH_2CH_3), 7.0-7.5(m,4,ArH),9.8(s,1,NH), 9.9(s,1,NH)
3-ClC_6H_4	78	159.5-161[f]	3250(N-H),1670,1660(C=O), 1620(C=C)	1.2(t,3,CH_3),1.9(m,2,4-CH_2), 2.4(m,2,5-CH_2),3.1(m,2,3-CH_2), 4.2(q,2,CH_2CH_3),6.9-7.3 (m,3,ArH),7.7(m,1,ArH),9.8 (s,1,NH),10.1(s,1,NH)
4-ClC_6H_4	63	129.5-130.5[h]	3450,3280(N-H),1680,1660(C=O), 1620(C=C)	1.2(t,3,CH_3),1.9(m,2,4-CH_2), 2.4(m,2,5-CH_2),3.1(m,2,3-CH_2), 4.2(q,2,CH_2CH_3),7.3-7.8 (m,4,ArH),9.9(s,1,NH), 10.2(s,1,NH)

[a]Satisfactory microanalytical data (±0.20% for C,H,N) were obtained for all compounds listed on this table. [b]Mineral oil mulls. [c]Solutions in hexadeuteriodimethylsulfoxide containing tetramethylsilane as internal standard. [d]Recrystallized from aqueous methanol. [e]Lit.[14] mp 127-128°. [f]Recrystallized from ethanol. [g]Recrystallized from petroleum ether (bp 63-75°). [h]Recrystallized from methanol.

Table 2. 3-Aryl-6,7-dihydro-1H-cyclopentapyrimidine-2,4-(3H,5H)-diones (3)[a]

Ar	Yield(%)	Mp(°C)	IR(cm^{-1})[b]	^{1}H-NMR(ppm)[c,d]
Ph	61	280-281[e,f]	3180,3100(N-H),1720,1630(C=O)	1.9-2.3(m,2,$CH_2\underline{CH_2}CH_2$),2.4-2.9 (m,4,$\underline{CH_2}CH_2\underline{CH_2}$),7.0-7.5(m,5,ArH)
2-MeC_6H_4	71	216-219[e]	3200(N-H),1700,1640(C=O)	2.0(s,3,CH_3),1.8-2.2(m,2, $CH_2\underline{CH_2}CH_2$),2.3-2.8(m,4, $\underline{CH_2}CH_2\underline{CH_2}$),6.9-7.2(m,4,ArH)
3-MeC_6H_4	71	274-276[g,h]	3200,3100(N-H),1720,1640(C=O)	2.3(s,3,CH_3),1.8-2.2(m,2, $CH_2\underline{CH_2}CH_2$),2.4-2.8(m,4, $\underline{CH_2}CH_2\underline{CH_2}$),6.8-7.4(m,4,ArH)
4-MeC_6H_4	70	270-271[g]	3200,3100(N-H),1725,1640(C=O)	2.2(s,3,CH_3),1.8-2.2 (m,2,$CH_2\underline{CH_2}CH_2$),2.3-2.8 (m,4,$\underline{CH_2}CH_2\underline{CH_2}$),6.8-7.3 (m,4,ArH)
3-ClC_6H_4	72	288-290[g,i]	3200,3100(N-H),1730,1650(C=O)	1.8-2.3(m,2,$CH_2\underline{CH_2}CH_2$), 2.4-2.9(m,4,$\underline{CH_2}CH_2\underline{CH_2}$), 7.0-7.5(m,4,ArH)
4-ClC_6H_4	72	287-289[g,j]	3250,3100(N-H),1710,1650(C=O)	1.8-2.2(m,2,$CH_2\underline{CH_2}CH_2$), 2.4-2.9(m,4,$\underline{CH_2}CH_2\underline{CH_2}$), 7.1-7.6(m,4,ArH)

[a]Satisfactory microanalytical data (±0.30% for C,H,N) were obtained for all compounds listed on this table. [b]Mineral oil mulls. [c]Solutions in hexadeuteriodimethylsulfoxide containing tetramethylsilane as internal standard. [d]The ^{1}H-nmr spectra showed that compounds 3 formed persistent hydrates. [e]Recrystallized from aqueous ethanol. [f]Lit. mp 319-321° (Ref. 5), 278° (Ref.12), 288° (Ref. 14), 281.5-282° (Ref.15). [g]Recrystallized from ethanol. [h]Lit.[15] mp 276-277°. [i]Lit.[15] mp 293-295°. [j]Lit.[15] mp 296-297°.

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