HETEROCYCLIZATION REACTIONS WITH CARBODIIMIDES: SYNTHESIS OF FUSED 1,2,4-TRIAZOLES

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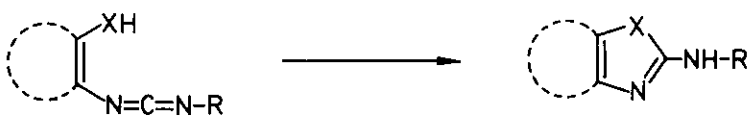
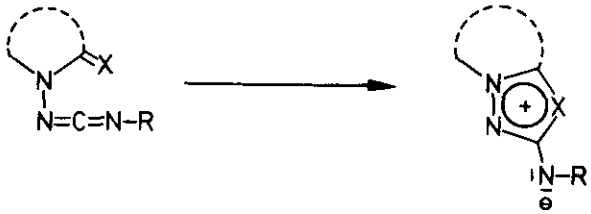
Abstract - *Several N-amino heterocyles react with diaryl carbodiimides under neutral conditions to give fused 1,2,4-triazoles. In some cases the intermediate heteroaryl guanidines are isolated, which by thermal or basic treatment cyclized to neutral or mesoionic fused 1,2,4-triazoles.*

Carbodiimides are one of the most important classes of compounds in organic synthesis both in the preparation of a variety of urea derivatives and also as condensing agents in the preparation of nucleotides and peptides. Carbodiimides are also useful synthetic intermediates in preparative heterocyclic chemistry. The two main routes to the preparation of heterocycles from carbodiimides are: a) intramolecular ring closure of aryl or heteroaryl carbodiimides; and b) reaction of carbodiimides with bifunctionalized alcohols or carboxylic acids.
In the first route, the cyclization may be achieved in three different ways:



Pathway A

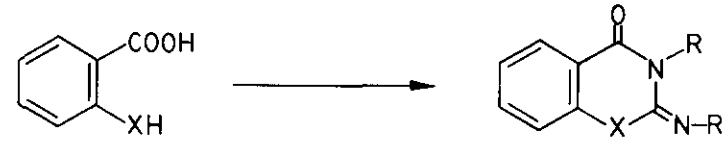
Pathway B



Pathway C

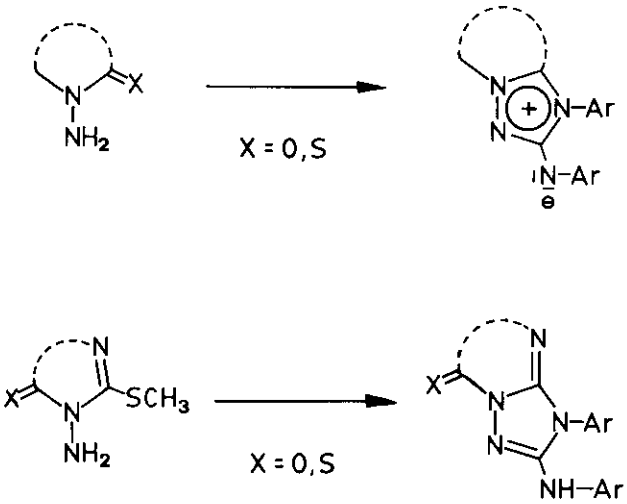
Pathway A allows the preparation of benzimidazole, benzoxazole and benzothiazole derivatives[1]. Pathway B is based on the thermal cyclization of conjugated carbodiimides to give fused heterocycles which contain the pyridine moiety[2,3]. Finally, N-heteroaryl carbodiimides undergo cyclization to fused mesoionic compounds derived from the 1,3,4-oxadiazolo[3,2-a]pyridine and 1,3,4-thiadiazolo[3,2-a]pyridine ring systems[4].

The second route is based on the reaction of carbodiimides with diols, aminoalcohols and aminomercaptans to give five membered heterocycles[5,6,7]. Similarly, carbodiimides react with ortho-substituted benzoic acids to give six membered derivatives[8,9,10]:



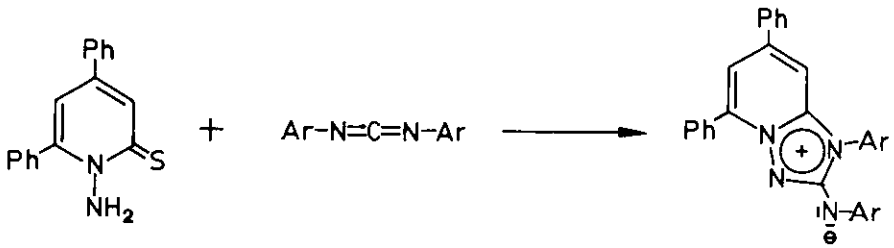
The structure of the reaction products between carbodiimides and carboxylic acids containing an amino group in the molecule depends on the kind of acid, and mainly on the substituent at the nitrogen atom.

As a continuation of our interest in the preparation of fused heterocycles bearing a 1,2,4-triazole moiety, we report now the reaction of several N-amino heterocycles with diaryl carbodiimides. The starting N-amino heterocycles are conveniently functionalized in at least one of the adjacent position to the endocyclic nitrogen atom. In general, the reaction of carbodiimides with N-amino heterocycles bearing a carbonyl or thiocarbonyl group leads to fused 1,2,4-triazoles which display mesoionic character; however, when a methylthio group is present on the heteroaromatic ring, the reaction products are found to be neutral fused 1,2,4-triazoles.



Fused Mesoionic 1,2,4-Triazoles

The N-amino heterocycle 1-amino-4,6-diphenylpyridine-2-thione 1 reacts with bis(4-bromophenyl)carbodiimide in dry toluene at reflux temperature for 15-20 h to give directly the mesoionic 1-(4-bromophenyl)-5,7-diphenyl-1,3,4-triazolo[3,2-a]pyridylium-2-(4-bromophenyl)aminide 2(Ar=4-Br-C_6H_4) as orange crystals in 52% yield[11]. On the other hand, 1-amino-4,6-diphenyl-2-pyridone 3 reacts with diphenylcarbodiimide under similar conditions to give a mixture of the mesoionic 2(Ar=C_6H_5) (30%) and the guanidine 4(Ar=C_6H_5) (35%)[12], which by thermal treatment at 250°C for 1 h leads to 2(Ar=C_6H_5) in 97% yield.



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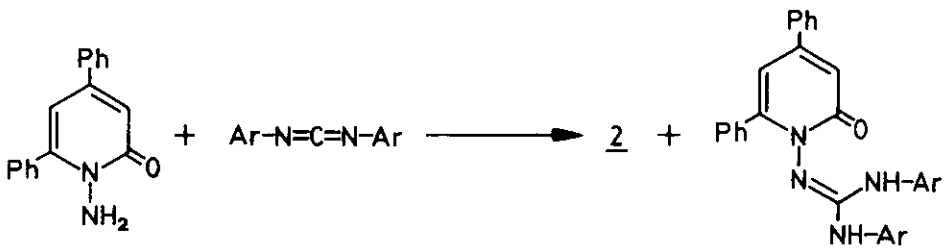
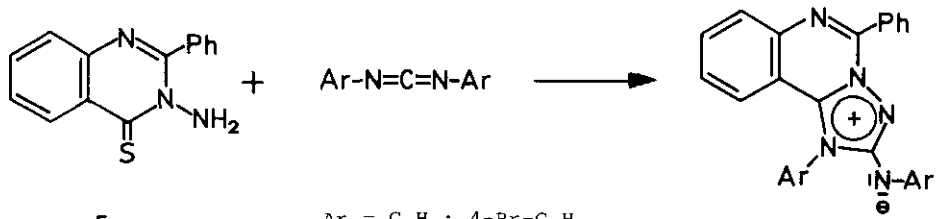


3 4

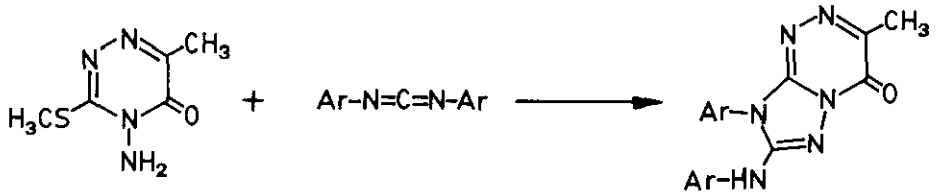
Similarly, 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline 5 reacts under similar conditions to give the new mesoionic compounds 1-aryl-5-phenyl-1,2,4-triazolo[1,5-c]quinazolylium-2-arylaminides 6(Ar=C_6H_5;4-Br-C_6H_4) as orange crystals in 53% and 36% yields respectively[13].



5 6

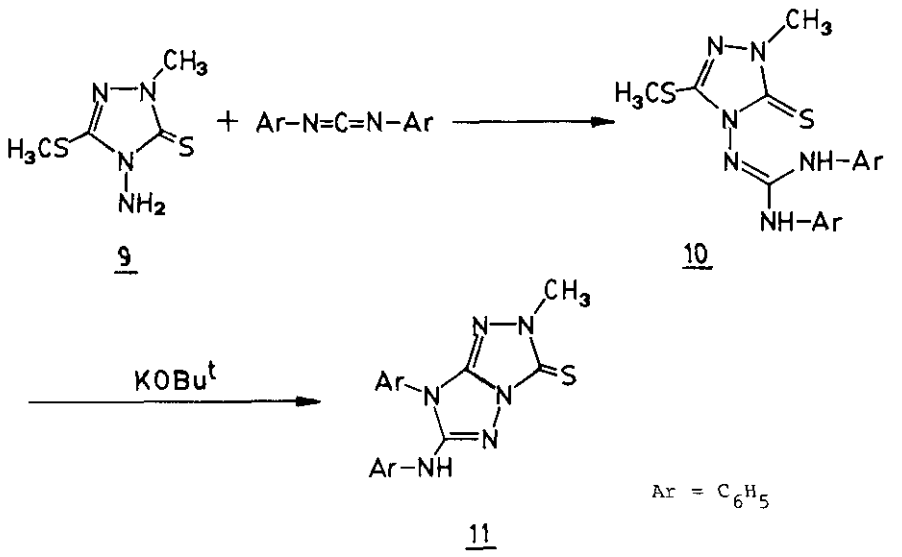
Fused Neutral 1,2,4-Triazoles

The N-amino heterocycle 4-amino-6-methyl-3-methylthio-5-oxo-4,5-dihydro-1,2,4-triazine 7 reacts with diaryl carbodiimides in dry toluene at reflux temperature for 40 h to give the corresponding 8-aryl-7-arylamino-3-methyl-8H-1,2,4-triazolo[5,1-c][1,2,4]triazin-4-ones 8(Ar=C_6H_5;4-Br-C_6H_4) in 55% and 62% yields respectively[14].



7 8

On the other hand, 4-amino-1-methyl-3-methylthio-5-thioxo-4,5-dihydro-1,2,4-triazole 9 reacts with diphenylcarbodiimide under similar conditions to give the heteroaryl guanidine 10(Ar=C_6H_5)[15] which undergoes ring closure by action of potassium t-butoxide in t-butanol as solvent to give 6-anilino-7-phenyl-2-methyl-3-thioxo-2,3-dihydro-7H-1,2,4-triazolo[4,3-b]-1,2,4-triazole 11(Ar=C_6H_5) in 85% yield[16].



9 10 11

These preliminary results show that the reaction of carbodiimides with N-amino heterocycles indeed can be used in the synthesis of fused heterocycles which contain the 1,2,4-triazole moiety. Further work in this way is in progress.

ACKNOWLEDGEMENT

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11. All the new compounds in this paper gave the satisfactory elementary analyses. Compound 2 (Ar= 4-Br-C_6H_4): Orange needles (toluene), m.p. 270-272°C, yield 52%. IR (ν, cm^{-1}, nujol): 1636 (m), 1608 (s), 1568 (s), 1495 (m), 1070 (m), 826 (s), 696 (s). MS (70 eV, m/z): 598 (M^++2, 49), 596 (M^+, 100), 594 (42), 582 (33), 580 (65), 578 (31), 459 (69), 457 (70), 426 (40), 424 (30), 402 (57), 401 (68), 400 (62), 399 (66), 319 (47), 263 (22), 165 (11).

12. For the analytical data of compound 2 (Ar= C_6H_5) see P. Molina, M. Alajarín, A. Arques, R. Benzal and H. Hernández, J. Chem. Soc. Perkin Trans. 1, 1984, 1891. Compound 4 (Ar= C_6H_5): White needles (toluene), m.p. 118-120°C, yield 35%. IR (ν, cm^{-1}, nujol): 3307 (s), 1648 (s), 1597 (s), 1563 (s), 1546 (s), 1495 (s), 1382 (s), 1297 (m), 1257 (m), 1076 (m), 872 (m), 764 (s), 753 (s), 696 (s). MS (70 eV, m/z): 456 (M^+,5), 438 (100), 437 (68), 422 (73), 364 (51), 363 (82), 261 (36), 218 (21), 194 (57), 93 (44), 77 (26).

13. Compound 6 (Ar= C_6H_5): Orange prisms (toluene), m.p. 295-297°C, yield 53%. IR (ν, cm^{-1}, nujol): 1614 (s), 1580 (s), 1563 (s), 1526 (m), 1516 (m), 1447 (m), 1292 (m), 1265 (m), 1197 (m), 1064 (m), 885 (m), 763 (s), 752 (s), 690 (s). MS (70 eV, m/z): 414 (28), 413 (M^+, 100), 412 (58), 397 (12), 337 (5), 296 (15), 294 (14), 208 (10), 205 (9), 102 (5), 77 (18). Compound 6 (Ar = 4-Br-C_6H_4): Orange needles (toluene), m.p. 334-335°C, yield 36%. IR (ν, cm^{-1}, nujol): 1599 (s), 1572 (s), 1545 (s), 1483 (m), 1387 (m), 1292 (m), 1196 (m), 1174 (m), 1065 (m), 1020 (m), 885 (m), 825 (s), 764 (s), 752 (s), 713 (s), 690 (s). MS (70 eV, m/z): 574 (14), 573 (48), 572 (43), 571 (M^+, 100), 570 (55), 569 (53), 568 (19), 557 (8), 555 (14), 553 (7), 492 (7), 491 (6), 490 (8), 374 (11), 295 (12), 294 (37), 205 (10), 102 (5).

14. For an alternative preparation of compounds 8 and their analytical data see P. Molina, M. Alajarín and J.R. Sáez, Synthesis, 1984, 983.

15. Compound 10 (Ar= C_6H_5): White prisms (benzene/hexane), m.p. 198-200°C, yield 65%. IR (ν, cm^{-1}, nujol): 3353 (m), 1619 (s), 1597 (s), 1580 (s), 1523 (s), 1489 (s), 1449 (s), 1347 (s), 1313 (m), 1245 (m), 752 (s), 743 (s), 702 (s), 694 (s). ^1H NMR (δ, $CDCl_3$, 60 MHz): 8.20 (1H, s), 7.8-7.1 (10H, m), 6.40 (1H, s), 3.90 (3H, s), 2.60 (3H, s). MS (70 eV, m/z): 371 (21), 370 (M^+, 93), 278 (11), 208 (17), 196 (11), 195 (82), 194 (100), 176 (87), 161 (20), 160 (17), 118 (37), 93 (64), 92 (49), 91 (29), 77 (69).

16. Compound 11 (Ar= C_6H_5): White prisms (dichloromethane/ether), m.p. 298-300°C, yield 85%. IR (ν, cm^{-1}, nujol): 3279 (m), 1642 (m), 1614 (s), 1586 (s), 1552 (m), 1495 (m), 1291 (m), 1183 (m), 975 (m), 753 (s), 719 (s), 685 (s). ^1H NMR (δ, DMSO-d^6, 60 MHz): 9.50 (1H, s), 8.0-7.1 (10H, m), 3.80 (3H, s). MS (70 eV, m/z): 323 (21), 322 (M^+, 100), 264 (16), 263 (11), 262 (47), 235 (14), 220 (20), 195 (14), 194 (17), 161 (23), 136 (27), 129 (17), 118 (33), 117 (15), 104 (13), 77 (28).

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