Pergamon

Tetrahedron Vol. 50, No. 23, pp. 6723-6726, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)E0318-N

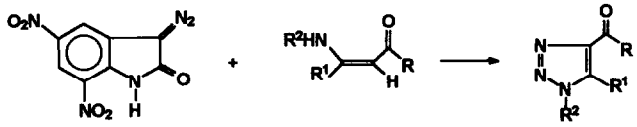
Bicyclic Triazoles From a Diazo Transfer Reaction Between Cyclic Enaminones and 5,7-Dinitro-3-diazo-1,3-dihydro-2H-indol-2-one

Rodinei Augusti and Concetta Kascheres*

Universidade Estadual de Campinas, Instituto de Química, Caixa Postal 6154, 13081 Campinas, São Paulo, Brazil.

Abstract: The synthetic usefulness of a new method of 1,2,3-triazole synthesis has been demonstrated. By employing cyclic enamino esters **3** and enamino ketones **4** in reactions with 5,7-dinitro-3-diazo-1,3-dihydro-2H-indol-2-one (**1**), bicyclic triazoles **5** and **6** have been prepared in good to excellent yields.

Introduction: Recently we reported a new synthesis of 1,2,3-triazoles by a diazo transfer reaction from 5,7-dinitro-3-diazo-1,3-dihydro-2H-indol-2-one (**1**) to acyclic enaminones (**2**) as shown.[1]



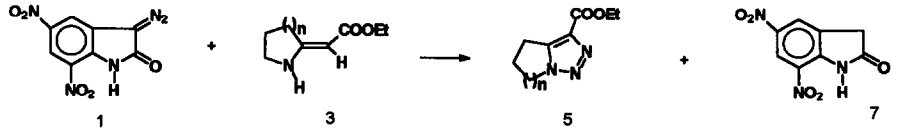
1 2

The ease of preparation of compound **1**[1] and enaminones[2], together with the absence of the problems associated with the most common method of triazole synthesis, i.e. the reactions of azides with alkynes,[3] makes this methodology extremely promissing. The structure of the enaminone determines unambiguously that of the triazole while avoiding the use of the potentially explosive alkyl azides.[4]

We envision the use of this reaction in the preparation of bicyclic triazole systems. The ability to form more highly nitrogenated analogs of aromatic compounds, like pyrroles or imidazoles, becomes important when one considers that as the number of heteroatoms in the ring increases, the tendency toward electrophilic attack decreases as does the reactivity of benzylic leaving groups toward substitution.[5] Pyrrole metabolites of pyrrolizidine alkaloids represent examples of compounds in which the high reactivity (and toxicity) of the pyrrole ring precludes their use in cancer chemotherapy.[6] Thus various attempts have been made to synthesize triazole analogs which modulate this reactivity downward.[7] With this in mind, the reactions of enamino esters **3** and enamino ketones 4 with **1** were undertaken.

Results and discussion: The reaction of **1** with **3a** (Table 1, entry 1) formed 3-carboethoxy-5,6-dihydro-4H-pyrrolo-[1,2-c][1,2,3]-triazole **5a** in 78% yield. This product can be used as a synthon to prepare triazole analogs of the tumor inhibitory pyrrolizidine alkaloid pyrrole metabollites.[7]

Table 1- Reactions of 5,7-dinitro-3-diazo-1,3-dihydro-2H-indol-2-one (1) with Enamino Esters 3.



1 3 5 7

entry	1	3	5 (% yield)	7 (% yield)	reaction time (hrs)*
1		3a (n = 1)	5a (78)	(57)	16
2		3b (n = 2)	5b (83)	(59)	16
3		3c (n = 3)	5c (73)	(55)	16

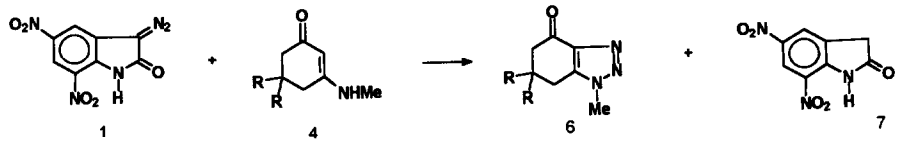
* In refluxing toluene

Enamino ester **3b** reacts similarly to form 3-carboethoxy-4,5,6,7-tetrahydro-[1,2,3]-triazolo-[1,5-a]-pyridine **5b** (Table 1, entry 2). There are only a few examples described in the literature for the synthesis of these systems[8] which are triazole analogs of the indolizidinic alkaloid skeleton. However, none of the methods permit the formation of the chemically useful carboethoxy derivative.

Enamino ester **3c** reacts with **1** to form 3-carboethoxy-5,6,7,8-tetrahydro-4H-[1,2,3]-triazolo-[1,5-a]-azepine (**5c**) in 73% yield (Table 1, entry 3). Apparently, there is only one example for the preparation of this class of compounds described in the literature. However, its synthesis through the reaction of N-nitroso tetrahydroazepine with benzonitrile[9] does not permit the formation of a derivative with a functional group like carboethoxy which is useful because of the chemical transformations which it can undergo.

In the reactions of **4a** and **4b**, there is the formation of **6a** (Table 2, entry 1) and **6b** (Table 2, entry 2) in approximately 50% yield, respectively. It is interesting to note that all examples of these systems in the literature are 1-aryl derivatives.[10]

Table 2- Reactions of 5,7-dinitro-3-diazo-1,3-dihydro-2H-indol-2-one (1) with Enamino Ketones 4.



1 4 6 7

entry	1	4	6 (% yield)	7 (% yield)	reaction time (hrs)*
1		4a (R = Me)	6a (50)	(34)	120
2		4b (R = H)	6b (49)	(40)	120

* In refluxing toluene

Although N_2 is the only portion of compound **1** which is incorporated into the products in this reaction, it is interesting to note that 5,7-dinitrooxindole (**7**) which is formed in all reactions could be used to prepare

1 by its reaction with azide and base[11].

In conclusion, the formation of these bicyclic triazoles in good to high yields under mild reaction conditions show that this synthetic method is both general and useful. These difficult to obtain products could prove to be interesting starting materials for the synthesis of therapeutically significant compounds.

Experimental: Melting points are uncorrected. Proton and carbon chemical shifts were measured relative to internal tetramethylsilane. The electron impact mass spectra were obtained at 70 eV. The enaminones 3[12], 4[13] and diazocarbonyl compound 1[1] were prepared according to reported methods.

General Procedure for Reactions of Diazocarbonyl Compound 1 with Enaminones 3 and 4. A solution of diazocarbonyl compound 1 (1 mmol) and enaminones 3 or 4 (1 mmol) in dry toluene (30 ml) was refluxed until the disappearance of the N_2 absorption band at 2100 cm^{-1} in the IR spectrum. The solvent was evaporated, and the crude material was submitted to column chromatography (Florisil) using mixtures of hexane, CH_2Cl_2, and methanol as eluents. All the products obtained were further purified by recrystallization.

3-carboethoxy-5,6-dihydro-4*H*-pyrrolo-[1,2-c][1,2,3]-triazole(5a). The product eluted with MeOH/CH_2Cl_2 (3:100) and formed colorless crystals, mp 65-6 °C (CH_2Cl_2/hexane): IR (KBr) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, 3H), 2.87 (m, 2H), 3.13 (t, 2H), 4.40 (m, 4H); MS *m/z* (relative intensity) 181 (14), 136 (22), 96 (47), 81 (100), 80 (65), 68 (42). Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; N, 23.19; H, 6.12. Found: C, 52.75; N, 22.98; H, 5.92.

3-carboethoxy-4,5,6,7-tetrahydro-[1,2,3]-triazolo-[1,5-a]-pyridine (5b). The product eluted with MeOH/CH_2Cl_2 (3:100) and formed colorless crystals, mp 88-90°C (hexane): IR (KBr) 1710 cm^{-1}; ^1H NMR (CCl_4) δ 1.39 (t, 3H), 1.93 (m, 2H), 2.07 (m, 2H), 2.95 (t, 2H), 4.27 (m, 4H); MS *m/z* (relative intensity) 195 (100), 150 (44), 110 (67), 98 (88), 80 (91), 67 (77), 55 (91). Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; N, 21.52; H, 6.71. Found: C, 55.05; N, 21.48; H, 6.46.

3-carboethoxy-5,6,7,8-tetrahydro-4*H*-[1,2,3]-triazolo-[1,5-a]-azepine (5c). The product eluted with MeOH/CH_2Cl_2 (3:100) and formed colorless crystals, mp 60-1°C (hexane): IR (neat) 1715 cm^{-1}; ^1H NMR (CCl_4) δ 1.40 (t, 3H), 1.72 (m, 2H), 1.84 (m, 2H), 1.93 (m, 2H), 3.19 (m, 2H), 4.28 (q, 2H), 4.45 (m, 2H); MS *m/z* (relative intensity) 209 (100), 163 (49), 98 (78), 80 (55), 67 (56), 55 (55). Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; N, 20.08; H, 7.23. Found: C, 57.75; N, 20.22; H, 6.87.

1,6,6-trimethyl-4,5,6,7-tetrahydro-1*H*-benzotriazol-4-one (6a). The product eluted with MeOH/CH_2Cl_2 (1:40) and formed colorless crystals, mp 131-2°C (lit.[1] 131-2°C).

1-methyl-4,5,6,7-tetrahydro-1*H*-benzotriazol-4-one(6b). The product eluted with MeOH/CH_2Cl_2 (1:40) and formed colorless crystals, mp 159-60 (CH_2Cl_2/hexane): IR (KBr) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (m, 2H), 2.60 (m, 2H), 2.91 (t, 2H), 4.04 (s, 3H); MS *m/z* (relative intensity) 151 (86), 122 (26), 94 (28), 67 (100).

5,7-Dinitro-1,3-dihydro-2*H*-indol-2-one (7). The product eluted with MeOH/CH_2Cl_2 (1:100) and formed

colorless crystals, mp 247-8°C (lit.[14] 248-50°C).

Acknowledgement: R.A. thanks FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) for financial support.

References and notes

1- Augusti, R.; Kascheres, C. *J. Org. Chem.* **1993**, *58*, 7079.

2- Greenhill, J.V. *Chem. Soc. Rev.* **1990**, *6*, 277.

3- (a) Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*; Ansell, M. F., Ed.; Elsevier: New York (NY), 1984; Vol. IV (D), Chapter 18. (b) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, p. 669.

4- Grundmann, C.; Haldenwanger, H. *Angew. Chem.* **1950**, *62*, 410.

5- For example, 1,2,3-triazoles are much less reactive than pyrroles in electrophilic aromatic substitution, see: Katritzky, A. R.; Lagowski, J. M. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, p. 39.

6- (a) Anderson, W. K.; McPherson, H. L.; New, J. S.; Rick, A. C. *J. Med. Chem.* **1984**, *27*, 1321. (b) Anderson, W. K.; Bhattacharjee, D.; Houston, D. M. *J. Med. Chem.* **1989**, *32*, 119. (c) Anderson, W. K.; Corey, P.F. *J. Med. Chem.* **1977**, 20, 812. (d) Mattocks, R. A. *J. Chem. Soc. Perkin I* **1978**, 896. (e) Ladurée, D.; Lancelot, J.; Robba, M.; Chenu, E.; Mathé, G. *J. Med. Chem.* **1989**, *32*, 456. (f) Anderson, W. K.; Chang, C.; McPherson, H. L. *J. Med. Chem.* **1983**, *26*, 1333. (g) Barbour, R. H.; Robins, D. J. *J. Chem. Soc. Perkin I* **1985**, 2475. (h) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L. T.; Moore, D.; Melder, D.; Powis, G. *J. Med. Chem.* **1985**, *31*, 1520. (i) Anderson, W. K.; Halat, M. J. *J. Med. Chem.* **1979**, *22*, 977. (j) Anderson, W. K.; McPherson, H. L. *J. Med. Chem.* **1982**, *25*, 84. (k) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L.T.; Fleischmann, T. J.; McGrowan, L. S.; Gordon, M. M. *J. Med. Chem.* **1985**, *28*, 687. (l) Anderson, W. K.; Corey, P.F. *J. Med. Chem.* **1977**, *20*, 1691. (m) Anderson, W. K.; Halat, M. J.; Rick, A. C. *J. Med. Chem.* **1980**, *23*, 87. (n) Lalezari, I.; Schwartz, E. L. *J. Med. Chem.* **1988**, *31*, 1427.

7- Pearson, W. H.; Bergmeier, S. C.; Chytra, J. A. *Synthesis* **1990**, 156.

8- Jones, G.; Sliskovic, R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York (NY), 1983; Vol. 34, p. 79.

9- Seebach, D.; Enders, D.; Rolf, D.; Reimund, P. *Chem. Ber.* **1977**, *110*, 1879.

10- Regitz, M.; Schwall, H. *Justus Liebigs Ann. Chem.* **1969**, *728*, 99.

11- Baum, J. S.; Shork, D. A.; Davies, H. M. L.; Smith, D. H. *Synth. Commun.* **1987**, *17 (14)*, 1709.

12-Celérier, J. P.; Deloisy, E.; Lhommet, G.; Maitte, P. *J. Org. Chem.* **1979**, *44*, 3089.

13- Chen, L. Y.; Mariano, P. S.; Little, G. M.; O'Brien, D.; Huesmann, P. L. *J. Org. Chem.* **1984**, *49 (2)*, 220.

14- Coretts, R. T.; Hindmarsh, K. W.; Mah, E. *Can. J. Chem.* **1970**, *48*, 3747.

(*Received in USA* 2 *March* 1994; *accepted* 29 *March* 1994)