SYNTHESIS OF NOVEL AND HARDLY-OBTAINABLE 1,2,3-TRIAZOLES WITH POTENTIAL ANTITUMORAL ACTIVITY BY A DIAZO-TRANSFER REACTION FROM 5,7-DINITRO-3-DIAZO-1,3-DIHYDRO-2H-INDOL-2-ONE TO ENAMINONES

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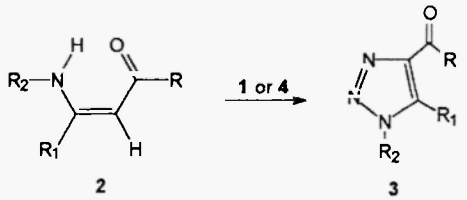
Abstract

Novel and barely accessible 1,2,3-triazoles with potential antitumoral activity were synthesized with good to moderate yields by a diazo-transfer process from 5,7-dinitro-3-diazo-1,3-dihydro-2H-indol-2-one to enaminones.

Introduction

In the last few years, the attention paid to 1,2,3-triazole systems has quickly increased. Some of these compounds have revealed several pharmacological activities such as antifungal, antibacterial, antiviral, anticonvulsive and some other potent inhibitory activities such as of HIV-1 reverse transcriptase (1). In a recent work, it was verified that a steroidal 1,2,3-triazole inhibited the growth of human prostate cancer cell lines in *in vitro* and *in vivo* experiments (2). Among the known preparation methods of the 1,2,3-triazole ring, the most common is the 1,3-dipolar cycloaddition reaction between substituted acetylenes and alkyl azides (3-5). Remarkably, solid-phase synthesis of functionalized triazoles by these cycloaddition routes was recently reported (6,7). Some years ago, an innovative methodology regarding the synthesis of simple 1,2,3-triazoles **3** was reported (8,9). Such procedure involves a transfer of two nitrogen atoms from 5,7-dinitro-3-diazo-1,3-dihydro-2H-indol-2-one **1** (9) to enaminones **2** (10), as displayed in Scheme 1. Another analogous method to prepare 1,2,3-triazoles recently reported consists in a diazo-transfer from mesyl azide **4** to enaminones **2** in the presence of sodium hydride (Scheme 1) (11).

Scheme 1

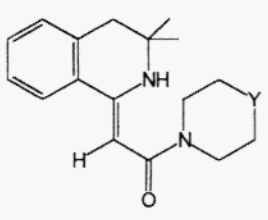


2 **3**

The uncomplicated preparation of diazo-transfer compounds (**1** and **4**) as well as enaminones **2** makes these methodologies extremely promising. Furthermore, these methods exhibit unique advantages, such as: avoiding the use

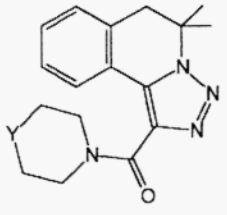
of explosive alkyl azides (12) and determining the structure of the desired 1,2,3-triazole unequivocally depending exclusively on the enaminone. The aim of the present paper is to investigate the generality and feasibility of using such diazo-transfer methodologies to synthesize novel polycyclic 1,2,3-triazoles with high lipophilicity and possible antitumoral activity. Bicyclic enaminones 5 synthesized according to the procedure described by Mikhailovskii et al. (13) were chosen because they offer an exclusive possibility to have access to the barely accessible 1,2,3-triazoles 7 (Scheme 2). In addition, it also makes it possible to compare (a) the efficiency of the diazo-transfer reactants (1 and 4) and (b) the reactivity of enaminones 5 with the analogous enamines 6 (Scheme 2).

Scheme 2



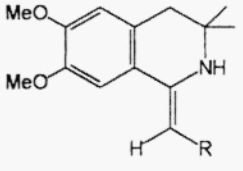
5

a) Y = O
b) Y= -CH_2CH_2-



7

a) Y = O
b) Y= -CH_2CH_2-



6

a) R = Ph
b) R= -$CH_2N(CH_2)_4$

Results and Discussion

Table 1 shows the results observed for the reactions between diazo 1 or mesyl azide 4 with enaminones 5 or enamines 6. Initially, the reaction between diazo 1 and enaminones 5a and 5b (entries 1 and 3) furnished, after a long reaction time (168 hours, 7 days), the corresponding 1,2,3-triazoles 7a and 7b in good yields (72% and 68%, respectively).

Table 1. Diazo-transfer reaction between 1 (14) or 4 (15) with enaminones (5 and 8) or enamines 6.

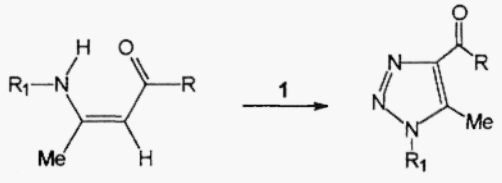
Entry	Reactant	Reaction with 1[a]	Reaction with 4[b]	Products and Yields (%)
1	5a	7 days	—	7a (72)
2	5a	---	7 days	No reaction
3	5b	7 days	---	7b (68)
4	5b	---	7 days	No reaction
5	6a	7 days	---	No reaction
6	6a	---	7 days	No reaction
7	6b	7 days	---	No reaction
8	6b	---	7 days	No reaction
9	8a	12 h	—	9a (73)
10	8a	---	7 days	No reaction
11	8b	12 h	—	9b (71)
12	8b	---	7 days	No reaction

[a] Molar ratio 1: 5/6/8 1:1, anhydrous refluxing toluene; [b] Molar ratio 4: 5/6/8: NaH 2.75:1:1.85, anhydrous acetonitrile, N_2 atmosphere.

It is noteworthy that in spite of the use of sterically hindered enaminones (5a and 5b), reactant 1 successfully transferred the diazo group to enaminones 5. It was also observed that enamines 6 did not react with diazo 1, even after several days in refluxing toluene. In all these situations, the starting materials were integrally recovered with no

detection of the corresponding 1,2,3-triazoles (Table 1, entries 5 and 7). This is an amazing result since it would be expected that owing to the higher nucleophilicity of enamines in comparison to enaminones, they should react with the electrophilic diazo-transfer agent 1 to produce the corresponding 1,2,3-triazoles in larger yields and in a shorter reaction time (9). In addition, it was also observed that mesyl azide 4, differently from reactant 1, was not effective as a diazo-transfer agent in reactions with either enamines 6 or even enaminones 5 (Table 1, entries 2, 4, 6, 8). Therefore, these results indicate that mesyl azide can be applied only to the synthesis of specific non-bulky N-substituted 1,2,3-triazoles. In an additional effort to corroborate the scope and the generality of the diazo-transfer methodology, it was investigated the reaction between the diazo-transfer agent 1 with enaminones 8, which contains bulky and lipophilic N-substituents (Scheme 3). In fact, in spite of these N-bulky substituents, the diazo-transfer reaction from 1 to 8 produced the corresponding 1,2,3-triazoles 9 in good yields and in a relatively short reaction time (12 hours) (Table 1, entries 9 and 11). In contrast, as previously mentioned, the diazo-transfer reaction between mesyl azide 4 and enaminones 8 was not observed. Even after a reaction time of seven days, there was no detection of the corresponding 1,2,3-triazoles 9 (Table 1, entries 10 and 12).

Scheme 3



8 9

a) R= Me; R_1= $C(Me)_3$ a) 73%

b) R= OEt; R_1= $Me(CH_2)_3CH(Et)CH_2$- b) 71%

Conclusion

This paper first reported on the synthesis of polycyclic 1,2,3-triazoles. It was also proved, in conjunction with previous studies (8, 9), the high efficiency and generality of the diazo-transfer process from 5,7-dinitro-3-diazo-1,3-dihydro-2H-indol-2-one 1 to any kind of enaminone, revealing that this synthesis methodology has a potential to be used in the preparation of novel and barely accessible 1,2,3-triazoles. Moreover, the investigation of the potential antitumoral activity of the 1,2,3-triazoles 7 and 9 is underway.

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(14) Typical experimental procedure (8,9): To 1 mmol of **1** in 50 mL of anhydrous toluene it was added 1 mmol of the enaminones (**5**, **8**) or the enamines (**6**). The reactional mixture was kept under reflux for 7 days. After filtration and solvent evaporation, the products (**7**, **9**) were isolated by chromatographic column (Florisil ®, eluent: hexane/dichloromethane 1:1 vol/vol) and further purified by TLC (eluent: hexane/dichloromethane 1:1 vol/vol).
7a - viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$) 8.02 –7.18 (m, 4H), 3.61 (t, 4H, *J*= 5.74 Hz), 3.39 (t, 4H, *J*= 5.45 Hz), 2.73 (s, 2H), 1.25 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) 190.88, 185.16, 168.35, 159.06, 136.78, 131.80, 128.39, 127.20, 126.03, 124.56, 56.09, 47.97, 44.92, 28.87, 27.32, 27.22. HRMS *m/z*: 312.16642 (Calcd. for $C_{17}H_{20}N_4O_2$: 312.16680).
7b - viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$) 7.97-7.19 (m, 4H), 3.72-3.00 (m, 10H), 2.73 (s, 2H), 1.26 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) 190.29, 183.42, 166.91, 136.52, 131.89, 129.96, 127.12, 127.01, 124.08, 56.06, 49.41, 44.92, 31.32, 28.87, 27.16, 16.19. HRMS *m/z*: 324.19543 (Calcd. for $C_{19}H_{24}N_4O$: 324.19490).
9a - colourless crystals; mp 62-63 °C (mp 62-63 °C, ref. 9);
9b - viscous oil; ^{1}H NMR (200 MHz,$CDCl_3$) 4.32 (q, 2H, *J*= 21.2, 6.2 Hz), 4.09 (d, 2H, *J*= 7.4 Hz), 2.48 (s, 3H), 1.82 (m, 1H), 1.30-1.13 (m, 11H), 0.81 (m, 6H). ^{13}C NMR ($CDCl_3$) 161.75, 137.99, 136.18, 60.69, 51.42, 39.69, 30.14, 28.28, 23.49, 22.73, 14.22, 13.82, 10.31, 9.03. HRMS *m/z*: 267.1941 (Calcd. for $C_{17}H_{20}N_4O_2$: 267.19485).

(15) Typical experimental procedure (11): To a stirred mixture of sodium hydride (20 mmol, 95%) in anhydrous acetonitrile (8 mL), under N_2 atmosphere at room temperature, it was added a solution of enaminones (**5**, **8**) or enamines **6** (3.70 mmol in 8 mL of anhydrous acetonitrile). After 0.5 h, it was slowly added a solution of mesyl azide **4** (5.0 mmol in 1 mL of anhydrous acetonitrile); stirring was kept for 48 h and the reaction was quenched with NaOH (10% w/w). The organic layer separated was dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure to give a residue which was extracted with methylene chloride (3 x 30 mL), and which was subsequently removed under reduced pressure.

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