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Investigation of regioselectivity in the synthesis of spiro [pyrrolidine-2,3′-oxindoles] by use of the Huisgen reaction

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Abstract The Huisgen reaction has been used to synthesize five-membered heterocyclic compounds in high yield and with high regio and stereoselectivity. In the synthesis of spiro [pyrrolidine-2,3′-oxindole] derivatives from isatin, α-amino acids, and (*E*)-*β*-phenyl nitroolefins, two regioisomers were obtained in each reaction. The regioselectivity of the major product was found to be different from that in reported work, and was investigated at the B3LYP/6-311G* level of theory. On the basis of this new finding, several conditions, for example molar ratio, solvent, and temperature, which affect the regioselectivity of this reaction were investigated; the results obtained are discussed. It was found that the regioselectivity of this reaction was affected by solvent and temperature, irrespective of the ratio of the reactants. Low temperature and high solvent polarity leads to high regioselectivity, and protic solvents result in higher yield and regioselectivity. These results are of benefit for regioselective synthesis of some compounds.

Keywords Huisgen reaction · Regioselectivity · Regioisomer · Spiro [pyrrolidine-2,3′-oxindole]

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Introduction

The Huisgen reaction, also known as 1,3-dipolar cycloaddition, has been used to synthesize many five-membered heterocyclic compounds [1–3]. Among these, natural product-like spiro-oxindole derivatives have attracted much intention because of their varied and potent bioactivity [2–6]. Because of their interesting bioactivity, many spiro-oxindole derivatives have been synthesized in our work [6–10]. In the Huisgen reaction of isatin, α-amino acids, and (*E*)-β-aryl nitroolefins, regioselectivity was different from that in other reported work; this was investigated by using the B3LYP/6-311G* level of theory [10]. The work is summarized in Fig. 1. In this paper, we provide more information about the factors affecting the regioselective synthesis of spiro-oxindole compounds by use of the Huisgen reaction.

Results and discussion

In our previous work, two regioisomers were obtained (**4a** and **4b**) in Huisgen reactions of isatin, proline, and (*E*)-β-phenyl nitroolefins. What was most interesting was that the major product (**4a**) had different regioselectivity from that of reported spiro-oxindole derivatives. In the major product, the nitro group shows correlation with C-4 of the newly constructed pyrroline and the phenyl groups connected to C-3. Theoretical study revealed there is an interaction, π–π stacking, between the azomethine ylide and the (*E*)-β-phenyl nitroolefin before reaction and the lower energy barrier between the stacking state and the transition state leads to the single

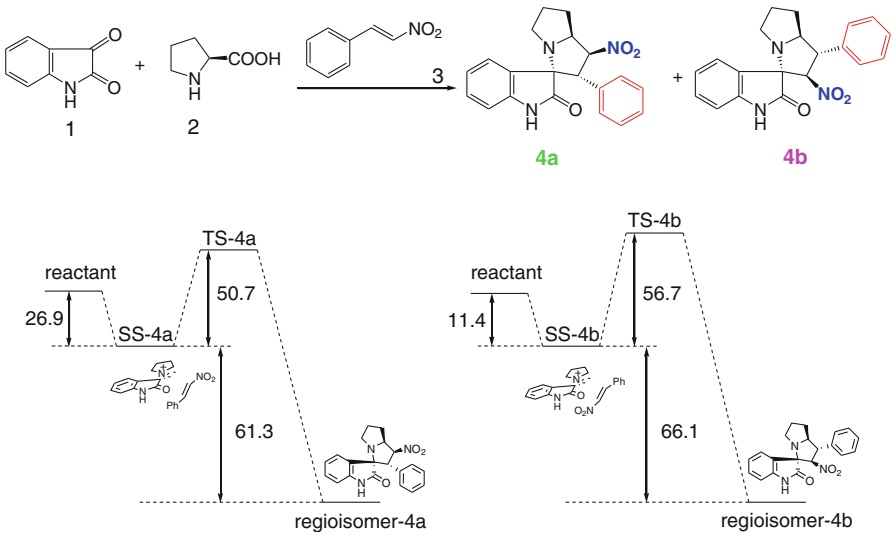


Fig. 1 Energy change (kJ/mol) of the Huisgen reaction between isatin, L-proline, and (*E*)-β-phenyl nitroolefins

or main product as described in Fig. 1. The stability of the stacking state of different conjugated systems with the oxindole group was determined from the calculations as: benzoyl group > ester group > phenyl group > nitro group. This mechanism was found to be applicable to all Huisgen reactions.

In synthetic practice, more attention should be paid to the conditions, especially the importance of molar ratio, solvent, and temperature in regioselectivity. So, in subsequent research, the molar ratio was studied first under typical conditions of room temperature (30 °C) in the solvent methanol–H_2O 3:1 (*v*/*v*), and reaction overnight; the results are shown in Table 1. It is apparent from this table that the total yield of **4a** and **4b** increases with increasing amount of (*E*)-*β*-phenyl nitroolefin. When the molar ratio is 1.2, the total yield is 89.7 %, and use of more (*E*)-*β*-phenyl nitroolefin does not improve the yield. The appropriate isatin–proline–(*E*)-*β*-phenyl nitroolefin molar ratio was therefore selected as 1:1:1.2. With different molar ratios the selectivity for **4a** and **4b** (i.e. **4a**:**4b**) hardly changed, in other words, the regioselectivity of this reaction is independent of molar ratio.

In the second step, the effect of reaction temperature on yield and regioselectivity was studied under the conditions isatin–proline–(*E*)-*β*-phenyl nitroolefin molar ratio 1:1:1.2, in the solvent methanol–H_2O 3:1 (*v*/*v*), and reaction overnight; the results were summarized in Table 2. Temperatures in the range 30 to 68 °C (b.p. methanol) were investigated; the results showed the total yield of **4a** and **4b** decreased as the temperature was increased. The reason might be increased side reactions in addition to the Huisgen reaction. It is remarkable that regioselectivity for **4a** decreased with the increasing temperature, because the different between the two energy barriers between the stacking states and the transition states is easier to overcome at high temperature. In other words, low temperature leads high yield and regioselectivity for **4a**.

The effect of methanol-to-H_2O volume ratio on the yield and regioselectivity was investigated under the conditions isatin–proline–(*E*)-*β*-phenyl nitroolefin molar ratio

Table 1 Effect of molar ratio on yield and regioselectivity

Isatin–proline–(*E*)-*β*-phenyl nitroolefin molar ratio	Yield (%) **4a**	Yield (%) **4b**	**4a**:**4b**
1:1:1.0	53.5	3.2	16.7
1:1:1.1	66.7	3.9	17.1
1:1:1.2	84.5	5.2	16.3
1:1:1.3	85.1	5.2	16.4

Table 2 Effect of temperature on yield and regioselectivity

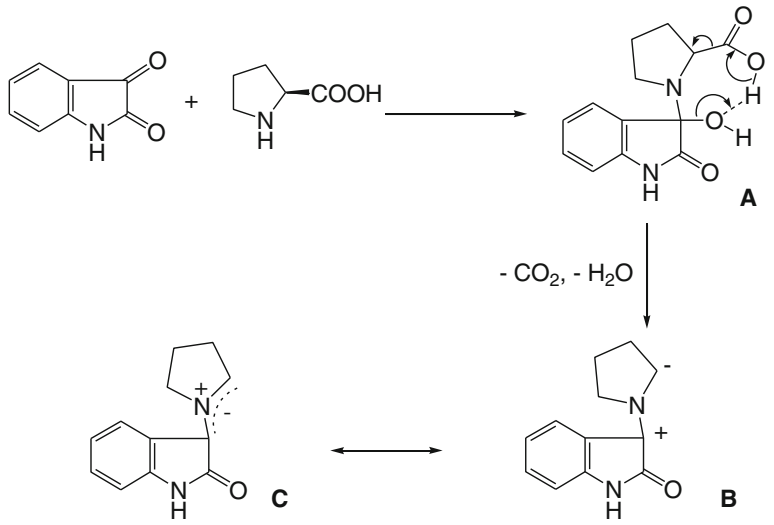
Temperature (°C)	Yield (%) **4a**	Yield (%) **4b**	**4a**:**4b**
30	84.5	5.2	16.3
40	82.6	6.5	12.7
50	73.8	7.5	9.8
60	71.9	8.6	8.4
68	67.6	8.5	8.0

Table 3 Effect of methanol-to-H_2O volume ratio on yield and regioselectivity

Methanol-to-H_2O volume ratio	Yield (%) **4a**	Yield (%) **4b**	**4a**:**4b**
100:0	60.4	24.6	2.5
100:1	58.7	18.5	3.2
50:1	62.8	15.6	4.0
10:1	70.4	10.4	6.8
3:1	84.5	5.2	16.3

1:1:1.2, at room temperature, and reaction overnight; the results are summarized in Table 3. It is apparent from the table that total yield decreases when a small amount of H_2O is added but then increases with increasing amount of H_2O. The regioselectivity, i.e. the ratio of **4a** to **4b**, changes substantially, from 2.5 to 16.3. Too much H_2O reduces the solubility of the (*E*)-*β*-phenyl nitroolefin, however, so more solvent has to be used.

It is common sense that the α-amino acid initially reacts with the isatin by a typical addition reaction to form intermediate A. The dipolarophile (intermediate B) is generated in situ via decarboxylative condensation of isatin with the α-amino acid, with simultaneous dehydration, yielding the azomethine ylide (intermediate C) which is a steady resonance hybrid of dipolarophiles (as shown in Scheme 1) [11, 12]. In this process, the decarboxylation and dehydration are the key steps, so the total yield decreases as a small amount of water is added, because of inhibition of dehydration. As the amount of water is increased, the polarity of the solvent increases, which helps to stabilize the dipolarophiles and/or azomethine ylide and leads to an increase in total yield. It can be found from experiments and theoretical analysis that high polarity benefits regioselectivity for **4a**.



Scheme 1 Process of formation of the azomethine ylide

Table 4 Effect of solvent on yield and regioselectivity

Solvent	Yield (%) **4a**	Yield (%) **4b**	**4a**:**4b**
Methanol	50.4	24.6	2.0
Ethanol	50.2	25.5	2.0
i-Propanol	49.7	17.6	2.8
n-Butanol	44.4	28.1	1.6
THF	41.8	12.5	3.3
Pyridine	39.7	18.2	2.2
Acetonitrile	32.7	19.8	1.7

Finally, the effect of the solvent on yield and regioselectivity was investigated under the conditions isatin–proline–(*E*)-*β*-phenyl nitroolefin molar ratio 1:1:1.2, at room temperature, and reaction overnight; the results are summarized in Table 4. Seven solvents were tested in this Huisgen reaction. The results show that total yields in the strong protic solvents methanol, ethanol, *i*-propanol, and *n*-butanol, are over 70 %, i.e higher than in weak protonic solvent, but regioselectivity is lower than that in THF, in which regioselectivity for **4a** was highest.

Conclusions

In conclusion, the regioselectivity of the Huisgen reaction of isatin, proline, and (*E*)-*β*-phenyl nitroolefins was affected by solvent and temperature, and was independent of the ratio of the reactants. Low temperature leads to high yield and high regioselectivity for **4a**, and high solvent polarity leads to high regioselectivity for **4a**. In addition, strong protic solvents result in higher yield and better regioselectivity for **4a**. We believe these effects of the reaction conditions will be similar in many regioselective Huisgen reactions.

Experimental section

General remarks

All starting materials and solvents (A.R. grade) are commercially available and were used without further purification. NMR spectra were recorded, in the solvents indicated below, on a Bruker DPX500 spectrometer, operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C; δ values are reported in ppm and J values in hertz. Mass spectra were recorded on a Micromass Platform II spectrometer, using the direct-inlet system operating in electron-impact (EI) mode.

General procedure for synthesis of spiro [pyrrolidine-2,3′-oxindoles]

The required (*E*)-*β*-phenyl nitroolefin was prepared by reaction of nitromethane with benzaldehyde in AcOH–$AcONH_4$ buffer. A solution of isatin (1 mmol),

α-amino acid (1 mmol), and (*E*)-β-phenyl nitroolefin (1.2 mmol) was heated under reflux in a specific solvent. When the isatin had been completely consumed (monitored by TLC), the solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, petroleum ether–ethyl acetate 4:1) to give the desired products.

4a: yield 8.5 %; ^{1}H NMR (D_6-acetone, 500 MHz), δ: 9.67 (1H, s), 7.55 (2H, d, $J = 7.5$ Hz), 7.48 (1H, d, $J = 7.5$ Hz), 7.41 (2H, m), 7.31 (2H, m), 7.04 (1H, m), 6.97 (1H, d, $J = 7.5$ Hz), 5.75 (1H, d, $J = 11.5$ Hz), 4.41 (1H, m), 3.93 (1H, m), 2.70 (1H, m), 2.56 (1H, m), 1.88–1.99 (4H, m); ^{13}C NMR (D_6-acetone, 125 MHz), δ: 178.2, 144.0, 138.3, 131.4, 129.8, 128.6, 128.5, 127.2, 124.0, 122.6, 111.3, 97.4, 73.7, 71.2, 54.0, 48.6, 31.1, 27.6; EI–MS, *m*/*z*: 349 (M^+), HRMS (ESI–TOF) calcd for $C_{20}H_{19}N_3O_3Na$, 272.1324; found, 272.1322.

4b: yield 73.1 %; ^{1}H NMR (D_6-acetone, 500 MHz), δ: 7. 87 (1H, d, $J = 7.5$ Hz), 7.23 (2H, m), 7.14 (3H, m), 7.07 (1H, m), 6.72 (1H, d, $J = 7.5$ Hz), 6.37 (1H, dd, $J = 10.5$, 9.5 Hz), 4.75 (1H, m), 4.57 (1H, d, $J = 11.0$ Hz), 3.37 (1H, m), 2.74 (1H, m), 2.02 (1H, m), 1.97 (1H, m), 1.74 (1H, m), 1.44 (1H, m); ^{13}C NMR (D_6-acetone, 125 MHz), δ: 178.0, 144.0, 134.4, 130.7, 129.4, 129.2, 128.5, 127.6, 126.1, 122.5, 110.6, 92.7, 75.7, 64.3, 52.9, 51.7, 28.6, 26.2; EI–MS, *m*/*z*: 349 (M^+), HRMS (ESI–TOF) calcd for $C_{20}H_{19}N_3O_3Na$, 272.1324; found, 272.1321.

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