Indian Journal of Chemistry
Vol. 37B, March 1998, pp. 277 - 280

Note

A new way for the synthesis of pyrazolo-1,5-benzodiazepinethiones from 3,3-dimercapto(or dialkyl-mercapto)-1-phenyl-2-propen-1-ones

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Received 28 August 1997; accepted (revised) 15 December 1997

New pyrazolo-1,5-benzodiazepinethiones have been synthesized by the condensation of 7-aminoindazole with 3,3-dimercapto(or dialkylmercapto)-1-phenyl-2-propen-1-ones.

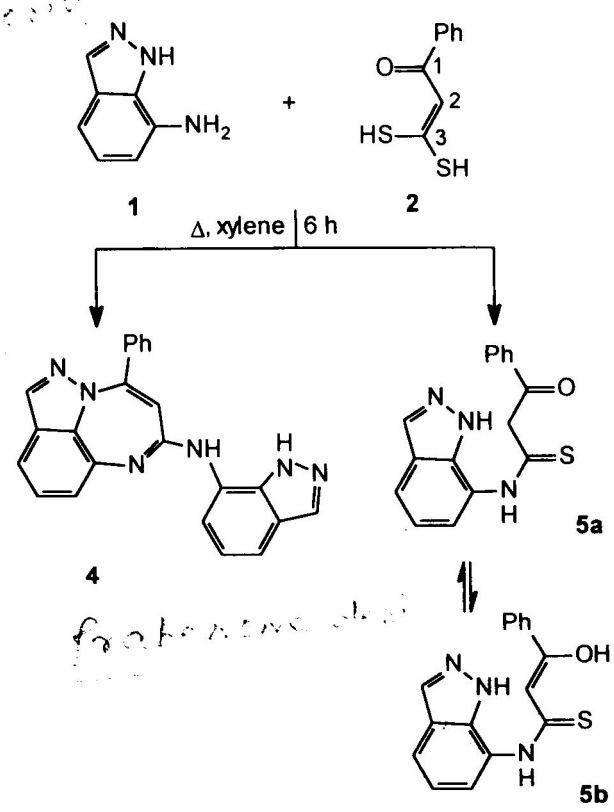
During our work to find new ways to synthesize derivatives of 1,5-benzodiazepine compounds,[1-3] we studied the condensation of 7-aminoindazole **1** with 3,3-dimercapto (or dialkylmercapto)-1-phenyl-2-propenone **2** (or **3a-b**). We report here that pyrazolobenzodiazepines can be prepared by condensing 7-aminoindazole with β-dicarbonyl compounds.[4]

The starting materials **2**, **3a-b** are easily prepared following the procedure described by Vialle *et al.*[5] These products can be used as 1,3-difunctionnal synthon for sulfur compounds.

Refluxing **2** with 7-aminoindazole **1** in xylene for 6 hr afforded the new product pyrazolo-1,5-benzodiazepine **4** and a thioamide by-product which exists under tautomeric forms **5a** and **5b** (Scheme I).

The products **4**, **5a-b** were identified by their spectral and analytical data. The ^{1}H NMR sectrum of compound **4** showed two signals at δ 8.00 and 8.10 ppm characteristic of pyrazolic protons as well as a signal at 5.08 ppm due to a vinylic proton.

The mass spectrum of compound **5** showed a major peak at m/z 105, which can be assigned to the



Scheme I

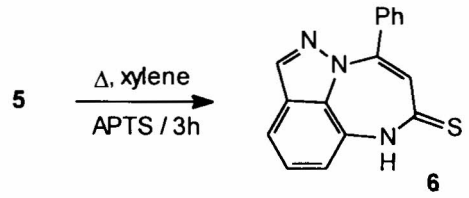
$C_6H_5CO^+$ ion indicating that the amino group of **1** is initially involved in the reaction attacking the C-3 carbon of compound **2**. This center seems to be more electrophilic than the carbonyl of the benzoyl group.

It is interesting to note that refluxing **5** for 3 hr with *p*-toluenesulfonic acid in xylene results in the formation of the pyrazolo-1,5-benzodiazepine-thione **6** (Scheme II).

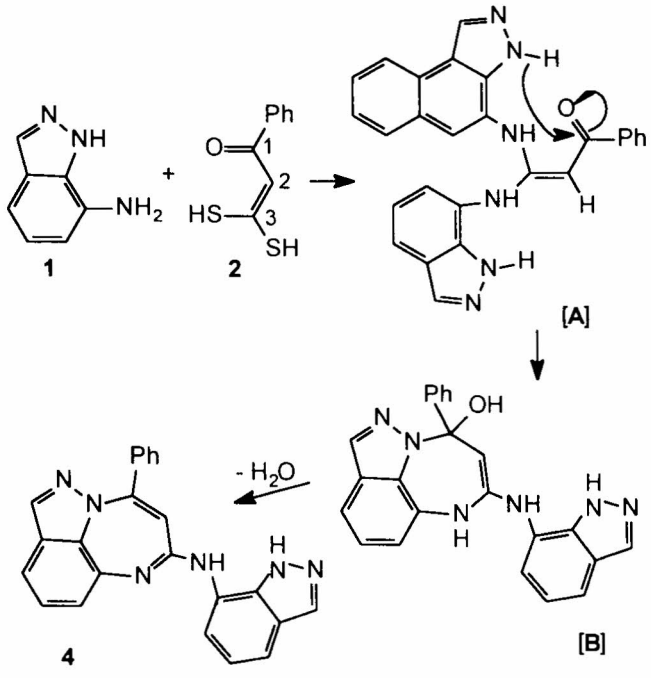
The structure of **6** was established by comparing its spectral data with those given in the literature.[2]

These results allowed us to propose a mechanism for the formation of **4**. It postulates that in the initial step two molecules of 7-aminoindazole attack on the C-3 of the reactant **2**. The intermediate [**A**] formed, undergoes intramolecular cyclization leading to an unstable compound [**B**] which loses a water molecule to give **4** (Scheme III).

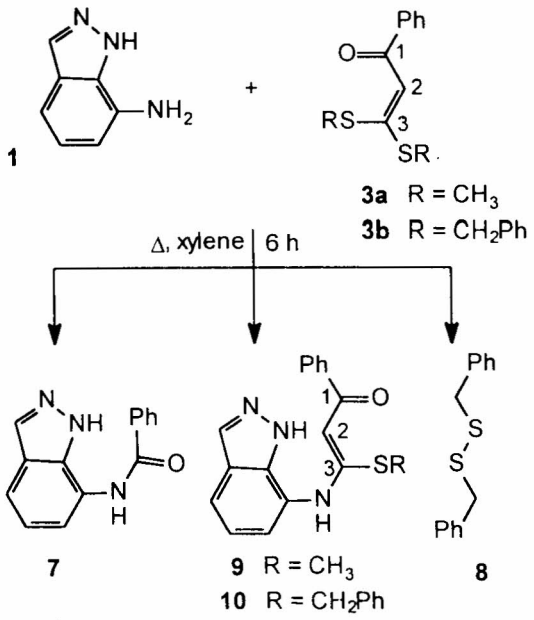
7-Aminoindazole **1** reacted with dialkylmercapto-



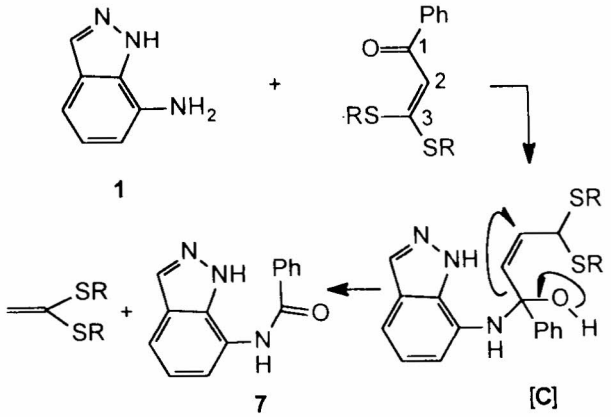
Scheme II



Scheme III



Scheme IV



Scheme V

phenylpropenones **3a-3b** under reflux in xylene for 6 hr giving three different types of products, 7-benzoylaminoindazole **7**, the sulfide **8** and α–crotonic type compounds **9** and **10** (Scheme IV). These compounds were identified on the basis of their spectral data.

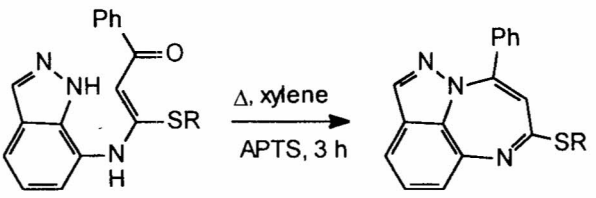
The ^{13}C NMR spectra of compounds **9** and **10** showed signals at δ 86.80 and 90.50 ppm, assignable to C-2 carbon. The signal at δ 186 ppm corresponded to the ketone carbon C-1. This indicates that the product was formed as a result of the condensation of the amino group of indazole **1** and the carbon at position-3 of the dialkylmercapto-phenylpropenones **3a** and **3b**.

The formation of compound **7** can be explained by an initial attack of the amino group of **1** on the ketonic function of **3**. The resulting intermediate is transformed into the product by loss of a molecule of 1,1′-dimercaptoethylene as shown in Scheme V.

Compounds **9** and **10** on treatment with *p*-toluene sulfonic acid in refluxing xylene gave exclusively the 6-alkylmercaptopyrazolo-1,5-benzodiazepines **11** and **12** respectively (Scheme VI). Their structures were assigned on the basis of their spectral data.

Another observation worth reporting is the reaction of 7-aminoindazole **1** with compounds **11** and **12** affording **4** (Scheme VII), previously prepared by another method (cf. Scheme III).

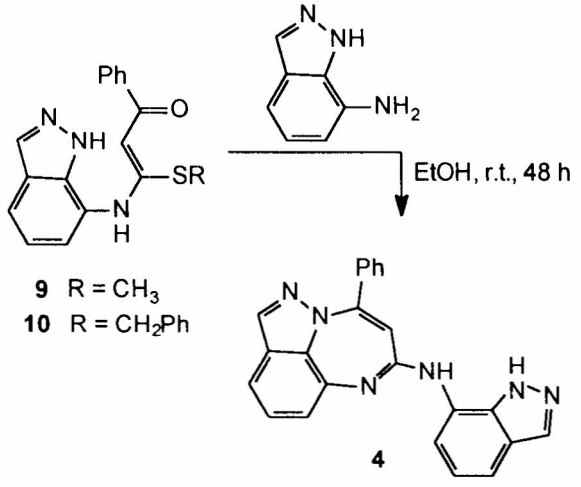
In conclusion we have described a new methodology for the synthesis of pyrazolo-1,5-benzodiazepinethiones from easily accessible starting materials.



9 R = CH_3
10 R = CH_2Ph

11 R = CH_3
12 R = CH_2Ph

Scheme VI



9 R = CH_3
10 R = CH_2Ph

Scheme VII

Experimental Section

General. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Spectra were recorded using the following instruments: IR, Perkin-Elmer 577 spectrometer (KBr disks); NMR, Bruker AC250 spectrometer (250 MHz for ^1H and 62.89 MHz for ^{13}C), chemical shifts are given in δ ppm downfield from TMS internal standard; MS (EI), Nermag R10-10C spectrophotometer.

Action of 7-aminoindazole 1 on 3,3-dimercapto-1-phenyl-2-propenone 2: To a solution of **1** (20 mmoles) in 150 mL of xylene, one equivalent of **2** in 15 mL of xylene was added. The reaction mixture was refluxed 6 hr and the solvent removed under vacuum. The resulting crude material was chromatographed over silica gel column using a 30:70 mixture of ethyl acetate and hexane as eluant to give the following compounds (**4** and **5**).

6-Indazolylaminopyrazolo[1,5,4-ef][1,5]benzodiazepine 4: This compound was obtained in 16% yield; m.p. 254-56°; IR (KBr): 1620, 1640 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): 5.08 (s, 1H), 6.81-7.62 (m, 6H), 8.00 (s, 1H), 8.12 (s, 1H), MS: m/z 376 ($M^{+\cdot}$); Anal. Calcd for $C_{23}H_{16}N_6$: C,73.40; H, 4.25; N, 22.34. Found: C, 73.37; H, 4.24; N, 22.31%.

Compound 5: It was obtained in 34% yield, m.p. 198-200°; IR (KBr): 3320 (OH), 3140 (NH), 1680 cm^{-1} (C=O); ^1H NMR (CF_3COOD): 4.40 (s, 2H), 6.30 (s, 1H), 6.60-7.60 (m, 3H), 7.80 (s, 1H); MS: m/z 295 ($M^{+\bullet}$).Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.08; H, 4.41; N, 14.24. Found: C, 65.05; H, 4.40; N, 14.23%.

4-Phenylpyrazolo[1, 5, 4-*ef*][1, 5]benzodiazepinethione 6: Compound **5** (0.01 mole) was dissolved in 120 mL xylene and 0.5 mg of *p*-toluenesulfonic acid added to it The reaction mixture was heated under reflux for 3 hr and the solvent removed under vacuum. The product obtained was purified by recrystallization from ethyl acetate to give **6** in 82% yield, m.p. 264-66°; IR (KBr): 1160 cm^{-1} (C=S); ^1H NMR (DMSO d_6): 5.51 (s, 1H), 6.81-7.62 (m, 3H), 7.90 (s, 1H)

Action of 7-aminoindazole 1 on dialkylmercaptophenylpropenones 3a-3b. The same procedure was employed as used in the reaction of **1** with **2**. Column chromatography of the product mixture over silica gel using CH_2Cl_2 as eluant.

Compound 7: It was obtained in 45% yield, m.p. 175-77°; IR (KBr): 1650 (C=O), 3220 cm^{-1} (NH); ^1H NMR ($CDCl_3$): 7.47 (s, 5H), 7.03-7.95 (m, 3H), 8.01 (s, 1H); MS: m/z 237 ($M^{+\cdot}$).

Compound 8: It was obtained in 40% yield, m.p. 69-71°; ^1H NMR ($CDCl_3$): 3.70 (s, 2H), 7.60 (s, 5H).

Compound 9: It was obtained in 65% yield, m.p. 106-08°; IR (KBr): 1580 (C=O), 3368 cm^{-1} (NH); ^1H NMR ($CDCl_3$): 2.06 (s, 3H), 5.73 (s, 1H), 7.10-7.93 (m, 8H), 8.13 (s, 1H), 11.45 (s, NH), 13.36 (s, NH); ^{13}C NMR($CDCl_3$): 86.80 (C-2), 170.03 (C-3), 186.02 (C=O); MS(EI): m/z 309 ($M^{+\cdot}$). Anal Calcd for $C_{17}H_{15}N_3OS$: C, 66.02; H, 4.85; N, 13.59. Found: C, 66.00; H, 4.84; N, 13.57%.

Compound 10: It was obtained in 68% yield,

m.p. 126-28°; IR (KBr): 1590 (C=O), 3370 cm^{-1} (NH); ^1H NMR ($CDCl_3$): 3.90 (s, 2H), 5.93 (s, 1H), 7.10-7.90 (m, 13H), 8.12 (s, 1H), 12.11 (s, NH), 13.45 (s, NH); ^{13}C NMR ($CDCl_3$): 36.42 (SCH_2), 90.45 (C-2), 168.19 (C-3), 186.45 (C=O); MS: m/z 385 ($M^{+\cdot}$). Anal Calcd for $C_{23}H_{19}N_3OS$: C, 71.69; H, 4.93; N, 10.90. Found: C, 71.67; H, 4.92; N, 10.88%.

Synthesis of the cyclized compounds 11 and 12: The same procedure as employed for the synthesis of compound **6** was used. The products were recrystallized from ethanol.

6-Methylmercaptopyrazolo[1,5,4-*ef*][1,5]benzodiazepine 11: It was obtained in 89% yield, m.p. 154-56°; IR (KBr): 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): 2.34 (s, 3H), 4.52 (s, 1H), 6.69-6.85 (m, 3H), 7.40 (s, 5H), 7.56 (s, 1H); MS: m/z 291($M^{+\cdot}$). Anal Calcd for $C_{17}H_{13}N_3S$: C, 70.10; H, 4.47; N, 14.43. Found: C, 69.98; H, 4.45; N, 14.42%.

6-Benzylmercaptopyrazolo[1,5,4-*ef*][1,5]benzodiazepine 12: It was obtained in 85% yield, mp. 160-62°; IR (KBr): 1630 cm^{-1} (C=N), ^1H NMR ($CDCl_3$): 4.18 (s, 2H), 4.35 (s, 1H), 6.66-7.29 (m, 3H), 7.35 (s, 5H), 7.54 (s, 1H); MS: m/z 367($M^{+\cdot}$). Anal Calcd for $C_{23}H_{17}N_3S$: C, 75.20; H, 4.63; N, 11.44. Found: C, 75.14; H, 4.62; N, 11.43%.

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