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A NEW AND CONVENIENT SYNTHESIS OF 3(2*H*)-PYRIDAZINONES BY REACTING CARBANION OF ETHYL TRIMETHYLSILYLACETATE WITH PHENYLHYDRAZONES

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Abstract: A one-pot synthesis of 5,6-disubstituted-2-phenyl-3(2*H*)-pyridazinones **4** is achieved on treatment of carbanion of ethyl trimethylsilylacetate with phenylhydrazones of 1,2-dicarbonyl compounds **1**.

There is considerable economical and biological interest in pyridazinones, since their derivatives are known to possess activities in a variety of fields.[1] The significant activities associated with pyridazinones has spurred much interest in the search for new methodologies for the synthesis of this class of compounds.[2] These observations and our continued interest[3] in the synthesis of pyridazinones and evaluation of their biological properties, prompted us to develop new methodology for the synthesis of various 5,6-disubstituted 3(2*H*)-pyridazinones. We would like to report a

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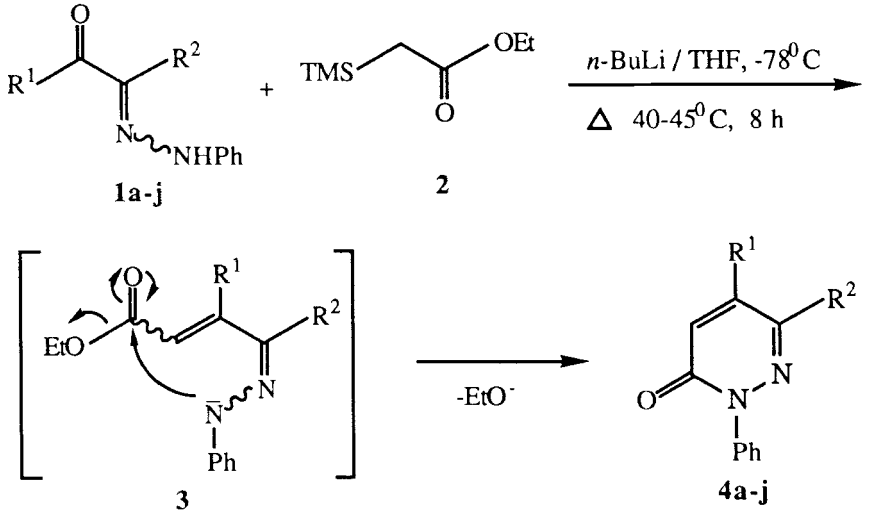

Scheme

convenient and one-pot synthesis of 3(2*H*)-pyridazinones using the carbanion of ethyl trimethylsilylacetate as a precursor.

Olefination of the carbonyl compounds is one of the most widely used reactions in organic chemistry. It can be effected by the Wittig reaction, by Peterson's (silyl-Wittig) reaction, using Tebbe's reagent, or by other less general methods.[4] It has become apparent that the Peterson's silyl-Wittig reaction is highly useful synthetic method for the preparation of olefins.[5] In most cases, the adducts of the trimethylsilylacetate carbanions and the carbonyl compounds spontaneously undergo dehydroxytrimethylsilylations to form the internal olefins. We herein report a ready adaptation of the Peterson olefination for the synthesis of 3(2*H*)-pyridazinones.

The mono phenylhydrazones of 1,2-dicarbonyl compounds[6] (**1a-j**) were treated with carbanion of ethyl trimethylsilylacetate at -78^0 C

Table: 5,6-Disubstituted -2-phenyl-3(2*H*)-pyridazinones **4a-j**

Compd No.	R^1	R^2	Yield@ (%)	m.p.[Lit] (°C)
2a	H	H	74	109-110[110-111][7a]
2b	H	Me	70	77-78[77.5-78][7b]
2c	Me	H	61	84[84-84.5][7c]
2d	Ph	Ph	18	234[233-234][7d]
2e	Me	COOMe	60	126-127[125-127][7e]
2f	Me	COOEt	58	102-103[102][7f]
2g	Me	CONHPh	52	258-259[259][7f]
2h	Me	$CONMe_2$	50	53-54[54][7f]
2i	Me	COMe	60	134[134][7g]
2j	Ph	COPh	20	181-182[182][7g]**2h**

@ All the compounds were purified by column chromatography using silica gel as stationary phase and gave satisfactory analytical figures and were characterized by spectroscopic means(i.r., mass and NMR).

for 1.5 h, -20° C for 1 h and 25° C for 2 h. This reaction mixture on heating at 40-45° C for 8 h in the presence of $NaHSO_4$ gave the directly cyclized product, 3(2*H*)-pyridazinones[3a,7] **4** in good yield. The compounds **4** were purified by column chromatography (Table). Good yields were obtained in most cases with the exception of pyridazinones **4d** and **4j** (R^1=Ph), probably due to steric hindrance by the bulky phenyl group to nucleophilic attack.

The cyclization process probably occurs through the formation of α,β-unsaturated ester (**3**) a Peterson's silyl-Wittig reaction.[5,8] The mechanism of the reaction is suggested to involve initial formation of adducts of trimethylsilylacetate carbanion and the phenylhydrazones

(**1**), which may undergo dehydroxytrimethylsilylation to form α,β-unsaturated ester **3** *in situ*. This intermediate **3** may undergo ring closure by intramolecular attack by the nitrogen anion to afford 3(2*H*)-pyridazinones **4** (Scheme).

The method reported herein provides an easy access to substituted 3(2*H*)-pyridazinones starting from the phenylhydrazcne of 1,2-dicarbonyl compounds and ethyl trimethylsilylacetate.

Experimental

THF was distilled from Na-benzophenone ketyl before use. Melting points were determined using a Buchi 510 apparatus and are uncorrected. IR spectra was recorded on a Perkin-Elmer FT-IR 1600 instrument. Proton NMR spectra were obtained on a Varian XL-200, 200 MHz spectrometer using TMS as an internal standard. A Jeol-JMS-OISG-2 mass spectrometer was employed for recording low resolution 75 eV mass spectra.

5,6-Disubstituted -2-phenyl-3(2*H*)-pyridazinones 4a-j

General Experimental procedure

A solution of dicyclohexylamine (4.0 mmol) in THF (20 mL) was placed in a 50-mL, three-necked round-bottomed flask equipped with condensor, magnetic stirring bar, a nitrogen inlet and a serum cap. The solution was cooled to -78^0 C and *n*-BuLi (4.05 mmol, 1.5 M in hexane) was added dropwise through a syringe. After stirring for 15 min at -78^0 C, a solution of ethyl trimethylsilylacetate (4.0 mmol) in THF (2.0 mL) was added dropwise and the resulting solution was stirred for 15 min at -78^0 C. To this solution was added dropwise a

solution of either phenylhydrazone **1a,b** (R^1=H, 2.0 mmol) or phenylhydrazone **1c-j** (R^1=Me or Ph, 1.3 mmol) in THF (5 mL) at -78^0 C. The reaction mixture was stirred at -78^0 C for 1.5 h, -20^0 C for 1 h and 25^0 C for 2 h. Finely ground $NaHSO_4.H_2O$ (0.75 gm) was added and the reaction mixture was stirred for 8 h at 40-45^0 C. The solid was filtered off, cold water was added, and the mixture was extracted with ethyl acetate (3 X 15 mL). The combined organic extracts were dried over sodium sulfate. Removal of solvents in vacuo and followed by column chromatography gave compound **4**; which was further purified by crystallization from appropriate solvent. Data of **4b**: IR (KBr), ν 1689 cm^{-1} (C=O), 1678 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 2.24 (s, 3 H, Me), 6.88 (q, 2 H, HC=CH), 7.48 (m, 5 H, Ph); MS (70 eV) m/z 186 (M^+, 18%). Data of **4i**: IR (KBr), ν 1712 cm^{-1} (C=O), 1684 cm^{-1} (C=O), 1675 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 7.44 (m, 5 H, Ph), 6.81 (d, *J* = 2 Hz, 1 H, HC=C), 2.62 (s, 3 H, COMe), 2.45 (d, *J* = 2 Hz, 3 H, 5-Me); MS (70 eV) m/z 228 (M^+, 28%). Data of **4j**: IR (KBr), ν 1708 cm^{-1} (C=O), 1686 cm^{-1} (C=O), 1678 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 7.51 (m, 15 H, Ph), 7.01 (s, 1 H, HC=C); MS (70 eV) m/z 352 (M^+, 36%). All compounds isolated gave satisfactory analytical figures and were characterized by spectroscopic means (IR, mass and NMR) and are consistent with our previous results.[3a]

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