was then quenched by addition of solid potassium carbonate (10 g) and H_2O (100 mL). The layers were separated and the organic phase was washed with H_2O (2 × 100 mL) and brine (100 mL). Drying (K_2CO_3), filtration, and removal of the solvent left a semisolid residue which was chromatographed on 100 g of silica gel (5% methanol in chloroform). The chromatographed residue was triturated with cold acetonitrile to give 1.4 g (74%) of analytically pure **1b**: mp 127 °C; IR ($CHCl_3$) 2950, 2800, 1600, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (2 H, m), 2.15 (4 H, m), 2.29 (3 H, s), 2.69 (1 H, m), 2.79 (1 H, d, J = 12), 2.87 (2 H, br d, J = 12), 7.17 (2 H, s), 7.30 (8 H, m). Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.87. Found: C, 87.28; H, 8.27; N, 5.07.

Resolution of (±)-(5*H*-*equatorial*)-1-Methyl-4-(3-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)piperidine (2a). A mixture of 2.78 g (7.55 mmol) of **(±)-2a** and 1.13 g (7.55 mmol) of *l*-tartaric acid was dissolved in 160 mL of boiling H_2O. The solution was filtered and then was allowed to cool slowly. The material that crystallized was removed by filtration, was washed with H_2O, and was collected and dried to afford 0.87 g of salt having mp 232–234 °C and $[\alpha]^{25}_{589}$ −31.6° (*c* 1.847, pyridine). The combined filtrate and washings were concentrated to approximately 90 mL and on cooling, an additional 0.26 g of salt having mp 228–232 °C, $[\alpha]^{25}_{589}$ −30.0° (*c* 1.122, pyridine), crystallized. The salts were combined to give 1.13 g of material that was used in Step A. The combined filtrates and washings were evaporated to dryness and were used in Step B.

Step A. The above salt (1.13 g) was recrystallized two times from H_2O to afford 0.67 g of material having a constant rotation: $[\alpha]^{25}_{589}$ −34.6° (*c* 1.641, pyridine), mp 239–239.5 °C. This salt was converted to the free base with saturated sodium bicarbonate solution, and it was then extracted into ether. The ether phase was washed with H_2O, dried ($MgSO_4$), and filtered, and the ether was removed. Recrystallization from acetonitrile gave **(+)-2a**: mp 178–180 °C; $[\alpha]^{25}_{589}$ +26.9°; $[\alpha]^{25}_{578}$ +29.0°; $[\alpha]^{25}_{546}$ +37.2°; $[\alpha]^{25}_{436}$ +126° (*c* 0.583, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}BrN$: C, 68.48; H, 6.02; N, 3.80. Found: C, 68.50; H, 6.15; N, 4.07.

Step B. The solid, obtained from evaporation of the combined filtrates and washings, was suspended in H_2O and was treated with a saturated solution of sodium carbonate. The mixture was extracted with ether to afford 0.85 g of free base. A mixture of this free base and 0.346 g of *d*-tartaric acid was dissolved in 26 mL of boiling H_2O. The material that crystallized on cooling was removed by filtration to give 0.56 g of salt having mp 231–234 °C and $[\alpha]^{25}_{589}$ +28.0° (*c* 1.38, pyridine). This material was crystallized twice from H_2O to give 0.26 g of salt having a constant rotation: $[\alpha]^{25}_{589}$ +34.1° (*c* 1.586, pyridine); mp 239–239.5 °C. This salt was converted into the free base as described in step A. Recrystallization from acetonitrile gave **(−)-2a**: mp 178–180 °C; $[\alpha]^{25}_{589}$ −27.4°; $[\alpha]^{25}_{578}$ −29.5°; $[\alpha]^{25}_{546}$ −38.0°; $[\alpha]^{25}_{436}$ −127° (*c* 0.559, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}BrN$: C, 68.48; H, 6.02; N, 3.80. Found: C, 68.46; H, 6.24; N, 3.87.

Equilibration of 1b and 2b to 1a and 2a. A sample of the desired 5H-axial compound (**1b** or **2b**) (4 mg) was dissolved in 0.5 mL of deuteriochloroform in an NMR tube at room temperature. The sample was then heated to the desired temperature in the NMR probe and the spectra were obtained every 730 s with a pulse angle of 60° and a repetition rate of 4 s. The reaction rate was measured from the appearance or disappearance of the 5*H*-benzylic methine proton by using the integrated intensity of the doublet to measure the amount of product/reactant present.

X-ray Crystallographic Analysis of 5*H*-Equatorial Conformer (+)-2a. Suitable crystals of **(+)-2a** for X-ray diffraction studies were formed from an acetonitrile solution. The space group symmetry was $P2_12_12_1$ with a = 9.663 (1) Å, b = 16.034 (2) Å, and c = 11.622 (2) Å for Z = 4. Of the 1439 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1313 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined with full-matrix least-squares techniques.[8] The assignment of the absolute configuration was established by applying the anomalous scattering contributions for the non-hydrogen atoms. The correct enantiomer had an R factor of 0.0669 while the incorrect one was 0.0713. This difference is significant at the 0.005 level[9] and was confirmed by careful remeasurement of 10 enantiomorph sensitive reflections. Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum \omega (|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.036. Tables I, II, and III (supplementary material) contain the final fractional coordinates, temperature parameters, bond distances, and bond angles.

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Supplementary Material Available: Tables containing the fractional coordinates, temperature parameters, bond distances, and bond angles for **(+)-2a** (4 pages). Ordering information is given on any current masthead page.

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Temperature-Dependent Alkylation of γ-Phenyl β,γ-Unsaturated Acid and Ester Systems in Hexamethylphosphortriamide–Tetrahydrofuran Solutions Using Lithium Diisopropylamide

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The reactivities of some β,γ-unsaturated carboxylic acids and their methyl esters toward alkylation with methyl iodide using the lithium diisopropylamide–hexamethylphosphortriamide (LDA–HMPT) system in THF have been investigated. The methylation selectivity of pent-3-enoic acid (**2**) and (1,2-dihydro-3-naphthyl)acetic acid (**6**) on using 1.0 equiv of methyl iodide is high, the α-mono- to α,α-dimethylation ratios at −78 °C being >20. The selectivity is substantially lower for styrylacetic acid (**4**) and increases with increasing temperature from 2.3 at −78 °C to 8.5 at −10 °C. The occurrence of dimethylation is ascribed to intermolecular proton exchange between the monomethylated species IIa and the nonmethylated species Ia. For the β,γ-unsaturated esters the methylation selectivity is somewhat higher than that for the corresponding carboxylic acids.

Alkylation of charge-stabilized carbanions derived from compounds containing a reactive methylene group leads in most cases to a mixture of mono- and dialkylated products. To avoid the dialkylation, specific methods

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Table I. Methylation of Acyl Derivatives via Their Lithium Salts in the Presence of HMPT with Methyl Iodide in THF

	substrate			reaction conditions			methylated products (%, ±1)			unreacted substr (%, ±1)
	R^1	R^2	R^3	HMPT	MeI (equiv)	T (°C)	α	α,α-di	γ	
				β,γ-Unsaturated Carboxylic Acids						
1[a,b]	H	H	H	–	1.0	−20	45	–	30	25
2	Me	H	H	+	1.0	−78	⩾95	trace	–	–
3[a,b]	Et	H	H	–	1.0	−20	85	15	–	n.d.[h]
4	Ph	H	H	+	1.0	−78	50	22	–	28
				+	2.0	−78	57	24	–	19
				+	1.0	−35	54	14	–	32
				+	1.0	−10	85	10	–	5
5[c]	Ph	Me	H	+	1.0	−30	95	⩽5	–	–
6			H	+	1.0	−78	90	⩽4	–	–
				+	1.0	−35	90	⩽6	–	–
7[c,d]			H	+	1.0	−78	>75	–	+	–
				+	1.0	−5	+	–	75	–
				β,γ-Unsaturated Esters						
8[e,f]	H	H	Et	+	1.0	−78	94	–	<3	–
g				+	1.0	0	87			
9	Me	H	Me	+	1.0	−78	>95	–	–	–
10	Ph	H	Me	+	1.0	−78	70	20	–	10
				+	1.0	−35	75	15	–	10
				+	1.0	−10	85	10	–	5
11			Me	+	1.0	−35	⩾95	⩽5	–	–
12[c]			Me	+	1.0	−30	⩾95	–	–	–
				+	1.0	−78	⩾95	–	–	–

[a] Reference 5. [b] The dianion was formed from the alk-2-enoic acid with 2.0 equiv of LDA. [c] Reference 6. [d] With 7 there is also methylation at the γ′-position. [e] Reference 3. [f] The anion was formed from ethyl crotonate and 1.0 equiv of LDA. [g] Reference 4. [h] n.d. = not determined.

depending on the nature of the carbanion were developed.[1-10] Recently the alkylation of several types of dianions was investigated with the emphasis on the regioselectivity of the reaction.[11,12]

In connection with our studies on the photochemistry of bi-[13] and trichromophoric[14] carbonyl compounds we required, amongst other compounds, mono-α-methylated γ-phenyl β,γ-enones. Application of the methylation method of van der Weerdt and Cerfontain[13] to 5-phenylpent-4-en-2-one led only to a very low yield of the mono-α-methyl derivatives; even when 1 equiv of methyl iodide is used, the main product is the α,α-dimethyl derivative (in addition to unconverted starting material). The required mono-α-methyl β,γ-enones can in principle be obtained readily from the corresponding α-methyl β,γ-unsaturated carboxylic acids.[15] In this paper we present the results on the methylation of a series of β,γ-unsaturated carboxylic acids and their methyl esters using the lithium diisopropylamide–hexamethylphosphortriamide (LDA–HMPT) system which acts as a strong base and chelates the formed anions.[3-5,16]

Occasionally γ-alkylation is encountered as a side reaction when both mono-[4,17] and dianions[5,18-20] are used as

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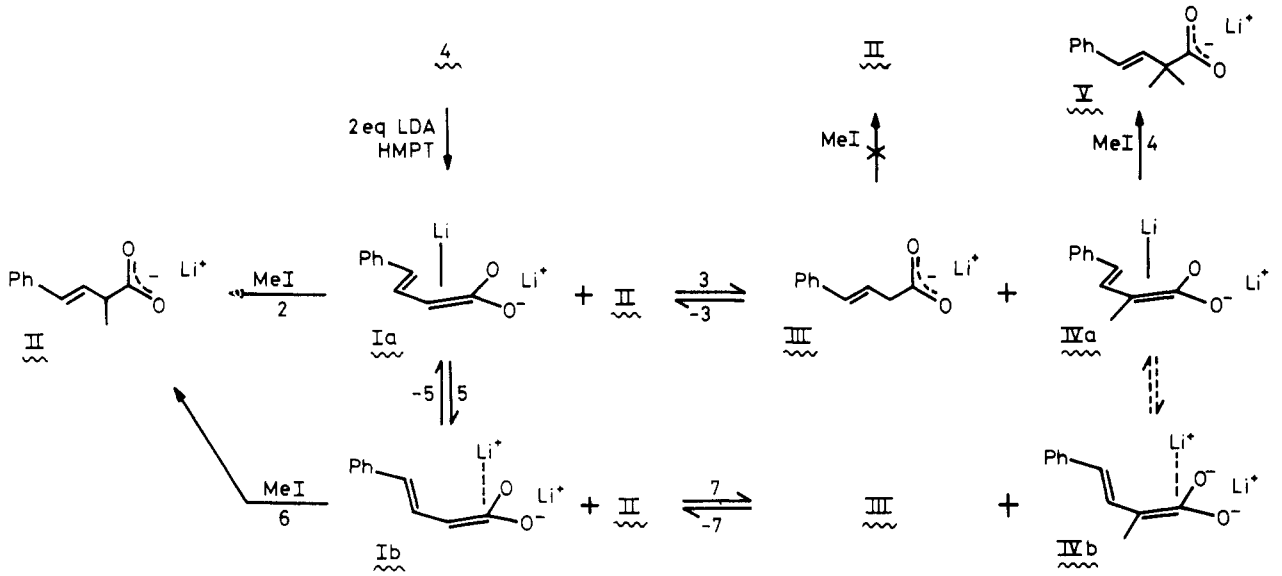
Scheme I. Mechanism of Methylation of γ-Phenyl β,γ-Unsaturated Carboxylic Acids



nucleophile, although it is the main process in a step of an indole synthesis.[12] In the methylation of 2-indenylacetic acid the ratio of γ- to α-alkylation increases with increasing temperature.[6] In the presence of added Cu(I) salts, the degree of γ-alkylation is strongly enhanced.[18,19]

Results and Discussion

Several β,γ-unsaturated carboxylic acids and their methyl esters are alkylated with methyl iodide when the LDA–HMPT system in THF is used as solvent.[5,6] The results are compiled in Table I together with some related literature data.

Carboxylic Acids. Methylation of (*E*)-pent-3-enoic acid (**2**) using 2.0 equiv of LDA as base in the presence of 2.4 equiv of HMPT with 1.0 equiv of methyl iodide at −78 °C leads via the lithium complexed dianion to (*E*)-2-methylpent-3-enoic acid as the *sole* product (Table I). Methylation of styrylacetic acid (**4**) under the *same* condition leads to only 50% of 2-methyl-4-phenylbut-3-enoic acid and 22% of 2,2-dimethyl-4-phenylbut-3-enoic acid. When 2.0 equiv of methyl iodide is used, the yields of the methylated product are somewhat higher, but the selectivity, i.e., the ratio of mono- to dimethylation, is the same. The phenyl group clearly reduces the nucleophilicity of the dianion, and apparently a high nucleophilicity of the dianion is a necessity for a selective methylation. When the temperature is raised, the content of monomethylated product of **4** increases to 85% at −10 °C. The methylations of (*E*)-3-methyl-4-phenylbut-3-enoic acid (**5**) and 2-indenylacetic acid (**7**) do not afford dimethylated carboxylic acids. At −5 °C **7** undergoes predominantly γ-methylation.[6] Methylation of (1,2-dihydro-3-naphthyl)-acetic acid (**6**) did not lead to dimethylated products beyond the limits of ^{1}H NMR detection, illustrating that the methylation of **6** is also highly selective.

The formation of the products may be explained in terms of the mechanism depicted in Scheme I for **4** as a typical substrate. The change in the selectivity of the methylation with variation in temperature may be ascribed to dissociation of the lithium dienolate species Ia into the dilithium dianion Ib (step 6), which is considered to be strongly temperature dependent in that the predominant species at the lower temperatures is the monoanion Ia and at the higher temperatures the dianion Ib. At *low* temperature Ia is thought to react with methyl iodide to yield the monomethylated lithium salt II (step 2) which species in turn reacts with the monoanion Ia by proton exchange with formation of the methylated monoanion IVa and the nonmethylated salt III (step 3). The anion IVa will now react with methyl iodide to the dimethylated lithium salt V (step 4). At the *higher* temperatures Ia dissociates into the dianion Ib (step 5). This ion will now only undergo methylation (step 6), the proton exchange with II (step 7) being considered relatively slow. Recently van Koten did point out to us that the variation in the reactivity of dienolates with temperature may be the result of a change of complexation with the lithium ion(s). At low temperature the dilithium salt of, e.g., styrylacetic acid is thought to use the six π electrons of the planar (*Z*,*E*)-oxypentadienyl anion moiety for complexation of one of the lithium ions,[21] the other one being ionicly bonded to the remaining carboxylate oxygen, as emphasized in structure Ia. The π-electron density is reduced and the methylation is therefore retarded. This allows proton exchange (step 3) and subsequent further methylation (step 4) to occur. With increasing temperature there will be rotation of the styryl moiety with respect to the carboxylate group (i.e., step 5). This will lead to a reduction of the strength of the association between the six π electron system and the lithium ion, whereas the complexation of the carboxylate moiety with the other lithium ion is unchanged (structure Ib).[22] The π-electron system will now be more nucleophilic and accordingly the methylation will be relatively fast, thus precluding the intermolecular proton exchange (step 7).

The effect of a β-substituent which leads to a reduction of the mono- to dimethyl substitution ratio (cf. the results of **4**–**7**) is ascribed to a rate reduction of step 3 due to steric hindrance[23] which will lead to an effective increase in the rate of step 4 relative to step 2.

The behavior of 2-indenylacetic acid (**7**) is not strictly comparable with that of **4**–**6**, as the acidity of the indenyl moiety [pK_a(indene) = 20[24]] will be substantially higher than that of the acetate moiety of **4**–**7**. This opens an

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additional ionization possibility for **7** which leads to γ'-methylation.[6] The temperature dependence of the α vs. γ regioselectivity may now be explained by presuming that the lower temperature methylation by step 2 leads mainly to α-methylation. At the higher temperature the conversion of Ia into Ib (step 5) is rapid relative to step 2 and the methylation now occurs by step 6 which yields predominantly the γ-methylated product.

Methyl Carboxylates. The methylation selectivity is somewhat higher for the β,γ-unsaturated esters than that for the corresponding carboxylic acids, as appears from a comparison of the mono- to dimethylation ratio of **10** with **4** (see Table I). The temperature dependence of the selectivity for the esters is similar to that of the corresponding carboxylic acids in that it increases with increasing temperature and may be explained along similar lines (cf. Scheme I), viz., in terms of a stronger rate enhancement for the monomethylation than the intermolecular proton exchange of the ester anion. Further the methylation selectivity is lower for **10** than for **8** and **9** due to the lower nucleophilicity of the anion of **10**.

Experimental Section

General Procedures for the Methylation of the Carboxylic Acids and Esters. A stirred solution of diisopropylamine (1.0 equiv) in 75 mL of THF cooled in an ice–salt bath was treated with a solution of *n*-BuLi (1.0 equiv, 1.5 M in hexane) by the syringe injection technique under nitrogen. After 15 min, 1.2 equiv of HMPT was added dropwise at −78 °C under stirring and the solution was stirred for 1 h. Then a solution of 0.5 equiv of acid or 1.0 equiv of ester (1.0 g in 20 mL of THF) was added slowly over 30–45 min. The solution immediately colored deep yellow in token of the formation of the (di)anion and after the addition the solution was stirred for another hour. Finally, the mixture was injected rapidly at the desired temperature (see Table I) with the required amount of methyl iodide. The reaction mixture decolorized to slightly yellow after 1 h, was quenched with wet THF, and was acidified with diluted hydrochloric acid (5%, 100 mL). The temperature was then raised to 10 °C and the solution extracted with ether. The organic layer was washed successively with 5% aqueous HCl (3 times), water, and brine and then dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure, leaving a yellow oil. The oil of the *acids* solidified. The solid (ca. 700 mg) was recrystallized from ligroin (bp 60–80 °C) to yield a white crystalline material (400–600 mg). The ^1H NMR spectrum of the purified material showed the same absorptions in almost the same ratios as the crude reaction mixture. The resulting *esters* (ca. 1.0 g) were separated by GLC.

The product ratios have been determined by multicomponent ^1H NMR analysis using as specific absorptions the signals of the α-methylene, the introduced methyl(s), the phenyl or benzo, and the vinyl hydrogens.

Pent-3-enoic acid (2) was prepared, as described for **4**,[25] by reaction of 9.4 g (0.159 mol) of propanal, 16.5 g (0.159 mol) of malonic acid, and a few drops diethylamine in 100 mL of ethanol to yield 9 g (59%) of pent-3-enoic acid (bp 66 °C (4 mmHg)) and 2.5 g (13%) of ethyl pent-3-enoate (bp 62 °C (20 mmHg)). **2**: ^1H NMR ($CDCl_3$, 60 MHz) (δ in ppm) 9.65 (br s, 1 H, CO_2H), 5.6 (m, 2 H, CH=CH), 3.1 (m, 2 H, CH_2), 1.7 (m, 3 H, CH_3); IR (liquid capillary, cm^{-1}) 3500–3000 (br, m), 2960 (m), 1700 (s), 1410 (m), 1290 (m), 1110 (m), 1040 (m), 970 (w).

2-Methylpent-3-enoic acid (13) was prepared by alkylation of **2** with 1.0 equiv of MeI at −78 °C in the presence of HMPT, in an isolated yield of 78%; ^1H NMR ($CDCl_3$, 60 MHz) (δ in ppm) 9.45 (s, 1 H, CO_2H), 5.50 (m, 2 H, CH=CH), 3.1 [m, 1 H, C(2)H], 2.3 [d, J = 7 Hz, 3 H, $C(2)CH_3$], 1.7 [m, 3 H, $C(5)H_3$]; IR (liquid capillary, cm^{-1}) 3500–3000 (br, m), 2970 (m), 2940 (m), 1700 (s), 1450 (m), 1405 (m), 1295 (m), 1100 (m), 1040 (m), 985 (w). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.93; H, 8.79.

2,2-Dimethylpent-3-enoic Acid. **13** was alkylated with 1.0 equiv of MeI at −78 °C to yield the dimethylated acid in 75% yield: ^1H NMR ($CDCl_3$, 60 MHz) (δ in ppm) 9.45 (s, 1 H, CO_2H), 5.5 (m, 2 H, CH=CH), 1.7 [m, 3 H, $C(5)H_3$], 1.25 [s, 6 H, $C(CH_3)_2$]; IR (liquid capillary, cm^{-1}) 3400–3100 (br, m), 2970 (m), 1700 (s), 1450 (m), 1385 (w), 1295 (m), 1120 (m), 1050 (m), 980 (w). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.70; H, 9.40.

4-Phenyl-3-butenoic acid (4),[25,26] methyl (*E*)-4-phenyl-3-butenoate (10),[13] and methyl 2-(1,2-dihydro-3-naphthyl)-ethanoate (11)[27] were prepared by reported procedures.

Methyl 2-methyl-4-phenylbut-3-enoate (14) and methyl 2,2-dimethyl-4-phenylbut-3-enoate (15) were prepared by methylation of **10** with 1.0 and 2.0 equiv of MeI, respectively, and purified by GLC on a copper column, 5 m × ¼ in., Chromosorb W-AW (60–80 mesh) coated with 15% DC-550 at 220 °C.

14: ^1H NMR (CCl_4, 60MHz) (δ in ppm) 7.3–7.0 (m, 5 H, C_6H_5), 6.40 (d, J = 16 Hz, 1 H, C_6H_5CH), 6.10 (dd, J = 6 and 16 Hz, 1 H, $C_6H_5CH{=}CH$), 3.60 (s, 3 H, OCH_3), 3.20 (m, 1 H, $CHCO_2H$), 1.30 (d, J = 7 Hz, 3 H, CH_3); IR (liquid capillary, cm^{-1}) 3100 (w), 3080 (w), 3040 (m), 3000 (m), 2960 (m), 1735 (s), 1600 (w), 1560 (w), 1500 (m), 1450 (m), 1435 (m), 1250 (m), 1170 (s), 970 (s), 750 (s), 695 (s). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.68; H, 7.36.

15: ^1H NMR (CCl_4, 60 MHz) (δ in ppm) 7.4–7.1 (m, 5 H, C_6H_5), 6.35 (s, 2 H, CH=CH), 3.65 (s, 3 H, OCH_3), 1.35 [s, 6 H, $C(CH_3)_2$]; IR (liquid capillary, cm^{-1}) 3080 (w) 3060 (w), 3030 (m), 2980 (m), 2950 (m), 1735 (s), 1600 (w), 1495 (w), 1470 (m), 1450 (m), 1430 (m), 1385 (w), 1250 (s), 1140 (s), 965 (s), 745 (s), 695 (s). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.00; H, 7.85.

2-Methyl-4-phenylbut-3-enoic acid (16) and 2,2-dimethyl-4-phenylbut-3-enoic acid (17) were prepared by saponification of the esters **14** and **15**, respectively, as described for **6** (see later).

16: ^1H NMR ($CDCl_3$, 100 MHz) (δ in ppm) 9.70 (br s, 1 H, CO_2H), 7.4–7.1 (m, 5 H, C_6H_5), 6.53 (d, J = 16 Hz, 1 H, C_6H_5CH), 6.27 (dd, J = 7 and 16 Hz, 1 H, $C_6H_5CH{=}CH$), 3.3 [br quintet, J = 7 Hz, 1 H, C(2)H], 1.37 (d, J = 7 Hz, 3 H, CH_3); IR ($CHCl_3$, cm^{-1}) 3300–2800 (br s), 2700 (br m), 1720 (s), 1650 (m), 1600 (w), 1500 (m), 1460 (s), 1420 (m), 960 (s), 740 (s), 680 (s). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.00; H, 6.88.

17: ^1H NMR ($CDCl_3$, 60 MHz) (δ in ppm) 10.2 (br s, 1 H, CO_2H), 7.4–7.1 (m, 5 H, C_6H_5), 6.4 (s, 2 H, CH=CH), 1.4 [s, 6 H, $C(CH_3)_2$]; IR ($CHCl_3$, cm^{-1}) 3050 (s), 2700 (br m), 1715 (br s), 1605 (m), 1495 (m), 1450 (s), 1405 (m), 1300 (m), 1140 (m), 955 (m), 850 (s), 675 (s). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.50; H, 7.38.

2-(1,2-Dihydro-3-naphthyl)ethanoic Acid (6). The ester **11** (4.0 g, 19.8 mmol) was saponified in 100 mL of 20% aqueous ethanol containing 10 g of KOH. The mixture was refluxed for 4 h and then cooled to room temperature. Normal workup yielded 3.4 g (91%) of **6**. Recrystallization from ligroin (bp 60–80 °C) afforded analytical material: mp 84–87 °C; ^1H NMR ($CDCl_3$, 60 MHz) (δ in ppm) 9.4 (br s, 1 H, CO_2H), 7.2–7.0 (m, 4 H, C_6H_4), 6.35 (br s, 1 H, C_6H_4CH), 3.20 (br s, 2 H, CH_2CO), 2.8 (m, 2 H, $C_6H_4CH_2$), 2.3 (m, 2 H, $C_6H_4CH_2{=}CH_2$); IR ($CHCl_3$, cm^{-1}) 3100 (br m), 2950 (m), 2850 (m), 2700 (br, w), 1695 (s), 1640 (w), 1480 (w), 1450 (w), 1400 (m), 1280 (m), 925 (w). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.47; H, 6.41.

Methyl 2-(1,2-dihydro-3-naphthyl)propanoate was prepared from **11** with MeI at −35 °C, as described in the general procedure. Preparative GLC (cf. **14** and **15**) afforded an analytical sample as a colorless oil: ^1H NMR (CCl_4, 60 MHz) (δ in ppm) 6.90 (m, 4 H, C_6H_4), 6.30 (br s, 1 H, C_6H_4CH), 3.60 (s, 3 H, OCH_3), 3.8–3.0 [m, 1 H, C(2)H], 3.5–3.0 (m, 2 H, $C_6H_4CH_2$), 3.0–2.5 (m, 2 H, $C_6H_4CH_2{=}CH_2$), 1.30 (s, 3 H, CH_3); IR (liquid capillary, cm^{-1}) 3070 (m), 3020 (m), 2980 (m), 2960 (s), 2955 (s), 2890 (m), 2840 (m), 1735 (s), 1490 (m), 1460 (s), 1440 (s), 1380 (m), 1335 (m), 1245 (s), 1205 (s), 1175 (s), 1090 (m), 890 (m), 765 (s). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 6.46. Found: C, 77.50; H, 6.51.

2-(1,2-Dihydro-3-naphthyl)propanoic acid was prepared by methylation of **6** at −35 and −78 °C following the general procedure to yield an analytical sample: mp 108–111 °C; ^1H NMR ($CDCl_3$, 60 MHz) (δ in ppm), 9.3 (br s, 1 H, CO_2H), 7.1–7.0 (m, 4 H, C_6H_4), 6.35 (br s, 1 H, C_6H_4CH), 3.30 [br q, J = 7 Hz, 1 H, C(2)H], 3.0–2.2

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(m, 4 H, CH_2CH_2), 1.35 (d, J = 7 Hz, 3 H, CH_3); IR ($CHCl_3$, cm^{-1}) 3200–2800 (br s), 1710 (s), 1650 (w), 1600 (w), 1490 (m), 1460 (m), 1310 (m), 990 (s). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.25; H, 7.27.

The acid was also obtained by alkylation of the ester **11** with MeI at −35 °C according to the general procedure followed by saponification of the resulting ester in a mixture of 20 g of KOH in ethanol–water (1:1, v/v).

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Registry No. **1**, 625-38-7; **1** (α-methylated), 53774-20-2; **1** (γ-methylated), 5204-64-8; **2**, 1617-32-9; **2** (α,α-dimethylated), 16642-52-7; **3**, 4219-24-3; **3** (α-methylated), 73513-50-5; **3** (α,α-dimethylated), 94041-92-6; **4**, 2243-53-0; **5**, 55131-28-7; **5** (α-methylated), 94041-93-7; **5** (α,α-dimethylated), 55078-29-0; **6**, 54154-71-1; **6** (α-methylated), 41791-34-8; **6** (α,α-dimethylated), 94041-94-8; **7**, 57932-05-5; **7** (α-methylated), 24040-29-7; **7** (γ-methylated), 69381-20-0; **8**, 1617-18-1; **8** (α-methylated), 1647-12-7; **9**, 818-58-6; **9** (α-methylated), 2258-55-1; **10**, 34541-74-7; **11**, 41791-31-5; **11** (α-methylated), 24040-31-1; **11** (α,α-dimethylated), 94041-95-9; **12**, 24040-30-0; **12** (α-methylated), 24040-28-6; **13**, 37674-63-8; **14**, 94041-87-9; **15**, 94041-88-0; **16**, 79164-23-1; **17**, 4405-27-0; $Me_2N^+{=}CH_2{\cdot}I$, 33797-51-2; MeI, 74-88-4; 2-cyclopentylidenecyclopentanone, 825-25-2; 2-(2-methylcyclopentylidene)cyclopentanone, 94041-89-1; crotyl chloride, 591-97-9; cinnamyl bromide, 4392-24-9; 2-(1-cyclopentenyl)-2-methylcyclopentanone, 43011-75-2; 2-(1-cyclopentenyl)-2-crotylcyclopentanone, 94041-90-4; 2-(1-cyclopentenyl)-2-cinnamylcyclopentanone, 94041-91-5; ethyl crotonate, 10544-63-5; propanal, 123-38-6; malonic acid, 141-82-2; ethyl pent-3-enoate, 1617-05-6.

Pyrimido[4,5-*c*]pyridazines. 6. Pyrimido[4,5-*c*]pyridazines and 1,2,4-Triazines from Reactions between 6-Hydrazinopyrimidin-4(3*H*)-ones and Vicinal Dicarbonyl Reagents

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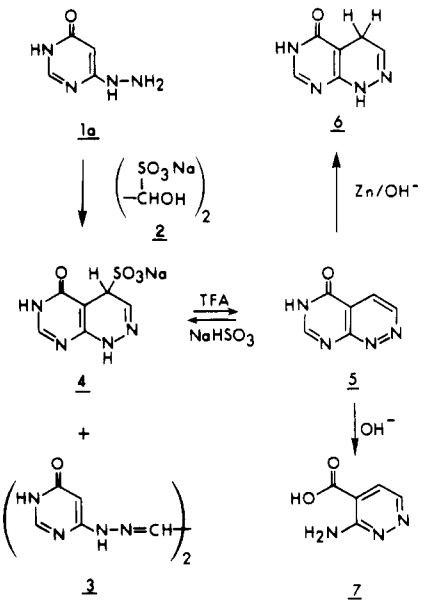
Reactions between 6-hydrazinopyrimidin-4(3*H*)-ones and selected vicinal dicarbonyl reagents have produced novel hydrazonopyrimidines, pyrimidopyridazines, and 1,2,4-triazin-5(2*H*)-ones. Criteria for the successful cyclizations, unexpected physical/chemical properties of the compounds, and a peculiar sodium salt are described.

Reactions of hydrazinopyrimidines with various vicinally functionalized reagents have been unpredictable. Depending upon the properties of both reactants, different products have resulted, including stable hydrazones, bis(hydrazones), pyrimido[4,5-*c*]pyridazines, pyrimido[4,5-*c*]-1,2-diazepines, and pyrrolo[2,3-*d*]pyrimidines.[1-5] Investigation of another hydrazinopyrimidine series has provided more unusual and sometimes unexpected chemistry. Selected reactions of 6-hydrazinopyrimidin-4(3*H*)-ones and vicinal carbonyl reagents are described in this paper. Properties of the products and some of their derivatives are also discussed.

Discussion

6-Hydrazinopyrimidinone **1a** and sodium bisulfite addition compound of glyoxal (**2**) reacted to give a mixture of bis(hydrazone) (**3**) and a pyrimido[4,5-*c*]pyridazine (Scheme I). The cyclization product was isolated as the bisulfite adduct **4**; however, bisulfite addition (determined by NMR to be 1,4) was readily reversible. Treatment of **4** with CF_3COOH liberated the heteroaromatic species **5**, which reverted to **4** in aqueous sodium bisulfite. As expected,[5] compound **5** was reduced to stable 1,4-dihydro derivative **6** with Zn/OH^-, but **5** is labile to aqueous base or boiling water alone. Treatment of **5** with refluxing 1 N NaOH for 1 h provided pyridazinecarboxylic acid **7**[6] in high yield (94%). Similar instability affects other compounds described in this paper.

Scheme I



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