^{3}H-estradiol [2,4,6,7-^{3}H(estradiol), 110 Ci/mmol), New England Nuclear] in TED buffer and 50 μL of 10^{-10}–10^{-5} M of competing ligand. The mixture was incubated for 18 h at 4 °C, and then 0.3 mL of DCC slurry (0.8% charcoal Norit A and 0.008% dextran in TED) was added to the tubes, and the contents were mixed. The tubes were incubated for 15 min at 4 °C and centrifuged at 800 × g for 10 min. An aliquot (200 μL) of the supernatant was removed and the radioactivity quantified by liquid scintillation spectrometry after addition of 5 mL of Aquasol-2 (New England Nuclear). Nonspecific binding was calculated by using 5 μM 17β-estradiol as competing ligand. Radioactivity was plotted as a function of the log concentration of competing ligand in the assay. The RBA was calculated as the ratio of the molar concentrations of estradiol and test compound required to decrease the amount of bound radioactivity by 50%, multiplied by 100.

Acknowledgment. We thank ICM for providing zearalenone and samples of zearalenols and zearalanols, the U.S. Agency for International Development for financial support, and David Bologa and T. Crick for technical assistance with the mass spectral studies.

Electrophilic Substitution Reaction at Azomethine Carbon Atom. Acylation of Aliphatic Aldehyde Hydrazones

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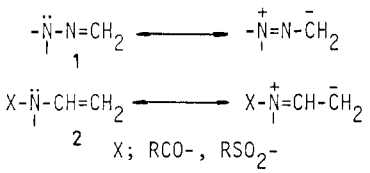
Received June 25, 1987

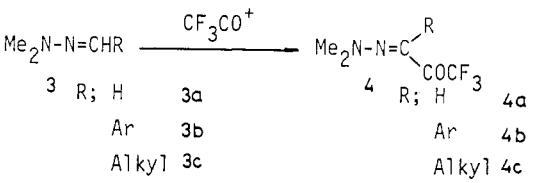
Formaldehyde dialkylhydrazones were found to undergo an electrophilic substitution reaction very easily at the azomethine carbon atom when treated with trifluoroacetic anhydride. Bistrifluoroacetylation is also possible. As an interesting extension of this reaction, trifluoroacetylation of dialkylhydrazones of aliphatic aldehydes and α,β-unsaturated aldehydes, was achieved. Similar reactions of these hydrazones with some other acylating reagents were also studied.

Introduction

Recent studies in this laboratory on the successful electrophilic substitution reaction at olefinic carbon atoms[1-8] prompted us to extend these works to hydrazone system. As for C=N linkage, hydrazones are quite different from imines in electronic character. In the case of imines, the C=N bond is polarized with positive charge at carbon and negative charge at nitrogen according to their inherent electronegativities. In contrast, in the case of hydrazone 1, conjugation of the C=N bond with adja-



cent nitrogen makes the azomethine carbon negatively charged. In this sense the azomethine carbon of hydrazone **1** is akin to the terminal olefinic carbon atoms of *N*-vinylcarboxamides or *N*-vinylsulfonamides **2**[3] and is expected to be acylated easily. In fact it was reported in our preceding paper[9] that the dimethylhydrazone of aromatic aldehydes **3b** can react with trifluoroacetic anhydride



(TFAA) at the azomethine carbon, i.e., electrophilic substitution reaction occurs there successfully. In order to establish this type of reaction more definitely, it become necessary to examine it with hydrazones of aliphatic aldehydes. As the simplest case, trifluoroacetylation of dimethylhydrazone of formaldehyde was studied first. Unusual resistance of **3c** toward TFAA was experienced in our preliminary experiments[9] and was the important problem to be solved in the present work. Reaction of **3** toward some other acylating reagents also attracted our interest.

Conversion of **3** to **4** is a key step of a series of transformations[9] from aldehydes to 1,2-dicarbonyl compounds **5**, as is illustrated in Scheme I.

Results and Discussion

Trifluoroacetylation of Formaldehyde Dimethylhydrazone (3a). On the basis of our semiempirical MO calculation carried out previously,[10] the reactivity of the azomethine carbon of **6a** toward electrophiles was estimated to be comparable to that of the β-carbon of **6b** as

(1) Hojo, M.; Masuda, R. *J. Org. Chem.* **1975**, *40*, 963.
(2) Hojo, M.; Masuda, R.; Kamitori, Y. *Tetrahedron Lett.* **1976**, 1009.
(3) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499.
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(6) Hojo, M.; Masuda, R.; Sano, H.; Saegusa, M. *Synthesis* **1986**, 137.
(7) Hojo, M.; Masuda, R.; Sakaguchi S.; Takagawa, M. *Synthesis* **1986**, 1016.
(8) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1986**, 1013.
(9) Kamitori, Y.; Hojo, M.; Masuda, R.; Fujitani, T.; Ohara, S.; Yokoyama, T. *J. Org. Chem.*, in press.
(10) Unpublished results.

(11) Our calculations carried out on the basis of CNDO/2 and MINDO/3 methods suggest the following. Although frontier electron density (HOMO) at the azomethine carbon of **6a** is estimated to be slightly less than that at the olefinic β-carbon of **6b**, the HOMO level of **6a** is higher than that of **6b**.

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Table I. Trifluoroacetylation of Formaldehyde Hydrazones 3a, 8a, 8b, 8c, and 8d

run	hydrazone[a]	TFAA, equiv	base,[b] equiv	$CHCl_3$, mL	condition	products	ratio,[c] %/%
1	**3a**	2	L, 2	2	0 °C, 3 min	**4a, 7a**	71/29
2		2	L, 2	4	0 °C, 3 min	**4a, 7a**	88/12
3		2	L, 2	8	0 °C, 3 min	**4a, 7a**	90/10
4		2	L, 2	12	0 °C, 3 min	**4a, 7a**	92/8
5		2	L, 2[d]	16	0 °C, 3 min	**4a**	(82)
6		6	L, 6	2	−40 °C, 30 min	**4a**	(66)
7		2	P, 2	2	0 °C, 1 min	**4a, 7a**	83/17
8		2	D, 2	4	0 °C, 1 min	**4a, 7a**	91/9
9	**8a**	1.5	L, 2	4	0 °C, 1 min	**9a**	(95)
10	**8b**	2	L, 2	8	0 °C, 3 min	**9b**	(97)
11	**8c**	2	L, 2	8	0 °C, 10 min	**9c**	(88)
12	**8d**	4	L, 2	8	30 °C, 24 h	**9d**,[e] **7b**	58/42

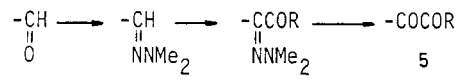
[a] In each case 2 mmol of hydrazone was used. [b] L, 2,6-lutidine. P, pyridine. D, Dabco. [c] Ratios were calculated on the basis of ^1H NMR spectra of crude materials and values in parentheses mean isolated yields. [d] In the absence of base the mixture of **4a** and **7a** (88/12) was obtained together with small amounts of unidentified products. Total weight of recovered materials was 186 mg. [e] Yield of **9d** after column chromatography was 51%.

Table II. Bistrifluoroacetylation of 3a

run	substrate, mmol	TFAA, equiv	base[a], equiv	solvent, mL	time,[c] days	products,[d] %				
						4a	**7a**	**10b**	**11a**	**12a**
1	**3a**, 20	2.5	L, 2	25	1	37	15	1	33	14
2	**4a**, 1	8	L, 4	5	1	42	0	0	24	34
3	1	4	L, 2	2	5.8	0	0	0	50	50
4	2	16	P, 4	2	3 h	11	0	15	46	28
5	2	4	D, 4	4	5	0	0	0	40	60
6	2	6	D, 6	3[e]	1	12	0	16	42	30
7	2	4	D, 4	4[f]	10	33	0	0	35	32
8	1	2		1	4	0	0	0	100	0
9	**7a**, 1	2.5	L, 2	2	5	0	100	0	0	0

[a] L, 2,6-lutidine. P, pyridine. D, Dabco. [b] $CHCl_3$ was used as solvent. [c] Reaction was carried out at 30 °C. [d] Ratios were calculated on the basis of ^1H NMR spectra of crude materials. [e] CH_2Cl_2 was used as solvent. [f] THF was used as solvent.

Scheme I



a model of vinyl ethers,[11] which had been found to react with TFAA easily to give β-(trifluoroacetyl)vinyl ethers in high yields. So we studied the reaction of **3a** with TFAA under conditions similar to the case of vinyl ethers. Expectedly this electrophilic substitution reaction proceeded smoothly and was completed within a few minutes even at −40 °C to give the corresponding trifluoroacetylated hydrazone **4a**. The results are summarized in Table I. In most cases, however, an undesirable N-acylated product (**7a**) was obtained as a byproduct together with **4a** (see

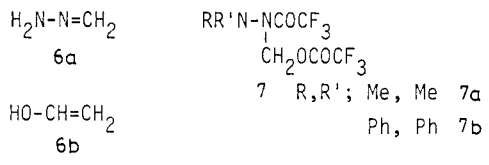
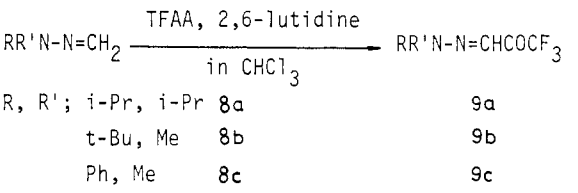


Table I). In our preceding paper[9] it was mentioned that an apparently unusual substituent effect observed in trifluoroacetylation (C-acylation) of para-substituted benzaldehyde dimethylhydrazones can be explained by concurrent competitive N-acylation. Although this N-acylation was ascertained only by ^1H NMR spectroscopy and the sole product was **4b** in the above case, the N-acylated product **7a** was actually isolated in the present case. The ratio of these products (**4a**/**7a**) varied considerably with the conditions employed, especially with temperature and the amount of solvents. The reaction carried out at −40 °C (run 6) showed better selectivity than that at 0 °C (run 1). Selectivity was also improved by dilution. With the use of more than 8 mL of $CHCl_3$ for 1 mmol of **3a**, formation of **7a** was suppressed completely (run 5). The reaction carried out in the absence of base afforded lower yields of **4a**.

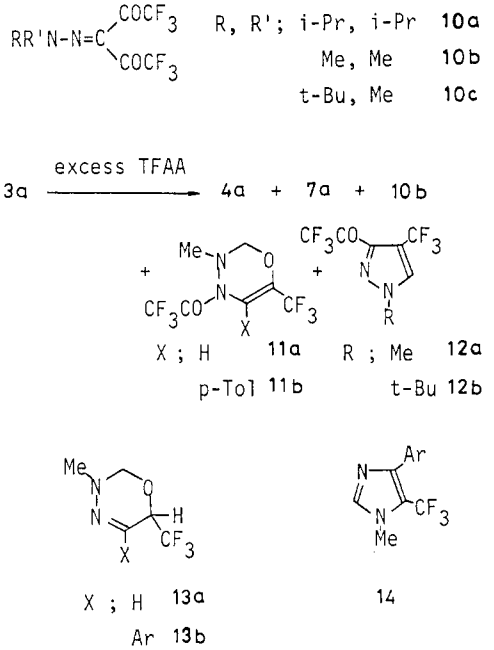
Trifluoroacetylation of formaldehyde diisopropylhydrazone (**8a**) was then examined, where two bulky isopropyl groups might inhibit undesirable N-acylation sterically. As was expected, the reaction of this hindered hydrazone proceeded very cleanly and the corresponding C-acylated product **9a** was obtained in fair yields without



any formation of the byproduct. Similarly, hindered hydrazones **8b** and **8c** also afforded **9b** and **9c** as the sole product, respectively. The reactions of **8d**, however, proceeded more slowly and gave **9b** together with considerable amounts of N-acylated product **7b**.

Bistrifluoroacetylation of Formaldehyde Hydrazones. We next directed our interest to the possibility that two trifluoroacetyl groups may be introduced to the azomethine carbon of formaldehyde hydrazones. To begin with, we examined the reaction of monoacylated diisopropylhydrazone **9a** with TFAA in excess. Surprisingly, the expected second acylation occurred smoothly and very cleanly to afford bistrifluoroacetylated hydrazone **10a** in good yield, although it was not so rapid as the first trifluoroacetylation (monoacylation) of **8a** to **9a**. Bistrifluoroacetylation (one step) of **8a** with the use of a large excess of TFAA also gave **10a**. On the other hand, attempted bistrifluoroacetylation (one step) of dimethylhydrazone **3a** gave somewhat complicated results (Table II). When **3a** was treated with 2.5 equiv of TFAA in the

presence of 2 equiv of 2,6-lutidine, five products were obtained: expected **10b** and **4a**, adduct **7a**, oxadiazine derivative **11a**, and pyrazole derivative **12a**. The structures of **10b**, **11a**, and **12a** were confirmed by IR, mass, and ^1H and ^{13}C NMR spectra and microcombustion analysis. As is seen in Table II the reaction of **4a** afforded **11a** and **12a** as major products, and **10b** as a minor product, although the ratio of them varied to some extent with the change of conditions. Yields of **10b** increased when pyridine or Dabco instead of 2,6-lutidine was used as a base (runs 4 and 6). Use of THF as solvent slowed down the rate of reaction considerably (run 7). Interestingly the reaction of **4a** without any bases afforded **11a** in a quantitative yield (run 8). The reaction of N-acylated compound **7a** resulted in complete recovery of the starting material (run 9). These results definitely indicate that **11a** and **12a** are produced from **3a** via **4a**.

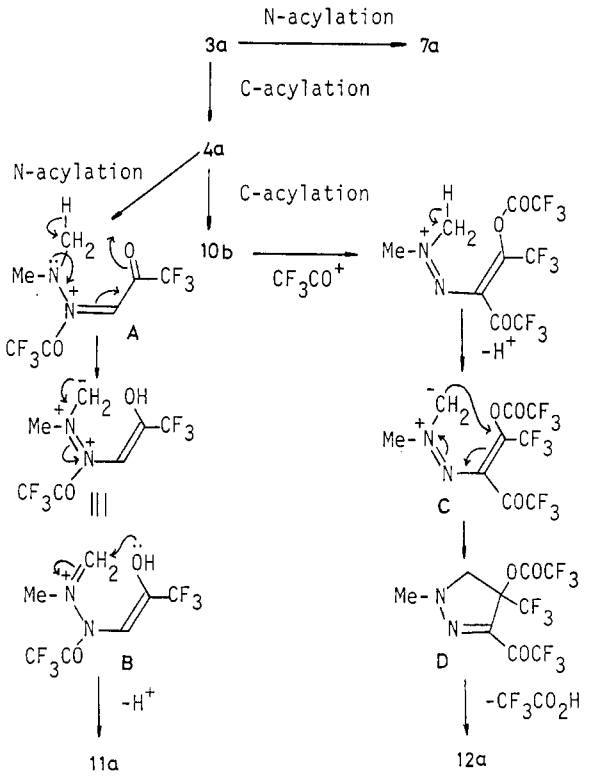


In our previous report[9] we described an interesting cyclization reaction of **4b** is induced thermally to give oxadiazine **13b** together with imidazole **14**. If this thermal transformation is also possible with **4a**, the resulting **13a** may be an intermediate leading to **11a** because N-acylation of **13a** and subsequent double-bond migration with deprotonation can afford **11a**. In order to check this possibility some experiments were performed. Under the conditions in which **4b** was converted **13b** and **14**, **4a** did not change at all and even under more enhanced conditions only decomposition of **4a** occurred to tarry materials. Attempted cyclization of **4a** to **13a** in the presence of trifluoroacetic acid or (and) 2,6-lutidine as catalyst resulted in complete recovery of **4a**. Conversion of **13b** (Ar = *p*-Tol) to **11b** by trifluoroacetylation was also tried and the result was again recovery of **13b** with small amounts of unidentified materials different from **11b**. These facts show that **13a** is not a precursor of **11a**.

Bistrifluoroacetylated hydrazone **10b** was found to be readily converted to pyrazole **12a** when **10b** was treated with 4 equiv of TFAA in the presence of 2,6-lutidine. This fact clearly indicates that **4a** is transformed to **12a** via **10b**. To our knowledge such a type of cyclization affording a pyrazole is the first case, although thermally induced cyclization giving imidazoles has been reported for **4b**[9] and for the monodimethylhydrazone of benzil.[12] The pyrazole

(12) Collibee, W. L.; Anselme, J.-P. *Tetrahedron Lett.* **1985**, *26*, 1595.

Scheme II



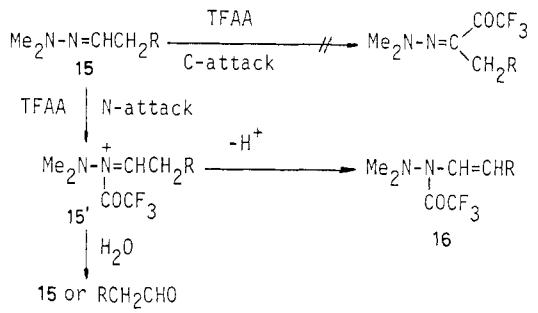
formation explains the facts that trifluoroacetylation of dimethyl derivative **4a** gave only small amounts of **10b** whereas that of diisopropyl derivative **9a** afforded **10a** in good yields. The transformation of **10b** to **12a** under the present reaction conditions is also consistent with the fact that **10b** could not be obtained from the prolonged reactions (run 3, 5, and 7).

On the basis of these experimental results a possible mechanism for the formation of **11a** and **12a** is shown in Scheme II. The key step for the oxadiazine formation from **3a** would be trifluoroacetylation of the azomethine nitrogen of **4a** followed by intramolecular prototropy of an *N*-methyl proton to trifluoroacetyl oxygen to afford B and subsequent ionic cyclization of B. As for the pyrazole formation, **4a** is trifluoroacetylated at the azomethine carbon to give bisacylated compound **10b** first, then deprotonated with the aid of a base to form *N*-methylide C, and finally, by ionic or pericyclic ring closure, pyrazole **12a** would be produced.

It was described earlier that **3a** can react with TFAA at both carbon and nitrogen to give **4a** and **7a**, respectively, while the reaction of **8a** with TFAA occurred selectively at carbon. This difference attributable to bulkiness of the two isopropyl groups of **8a** can be seen in the second trifluoroacetylation of **4a** and **9a**, too. Namely, although **9a** was selectively converted to **10a** by C-attack, **4a** was attacked on both carbon and nitrogen to afford small amounts of **10b** and much **11a** and **12a** (see Scheme II).

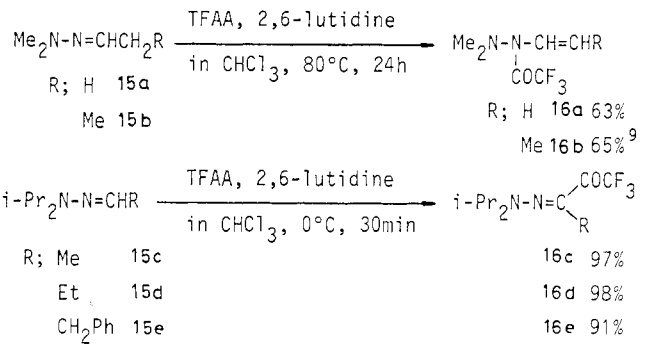
In the case of **9b**, on treatment with 8 equiv of TFAA in the presence of 3 equiv of 2,6-lutidine, **10c** and **12b** were obtained in 10% and 66% yields, respectively, and no oxadiazine derivative was detected. The bulkiness of the *tert*-butylmethylamino group was enough to surpress N-acylation necessary for the formation of an oxadiazine derivative. Because of gradual decomposition of **10c** during purification, **10c** could not be isolated in pure form. Reactivity of **9c** toward TFAA was much lower compared to **4a**, **9a**, and **9b** and it was recovered unchanged even by treatment with 6 equiv of TFAA for 24 h. The presence

Scheme III

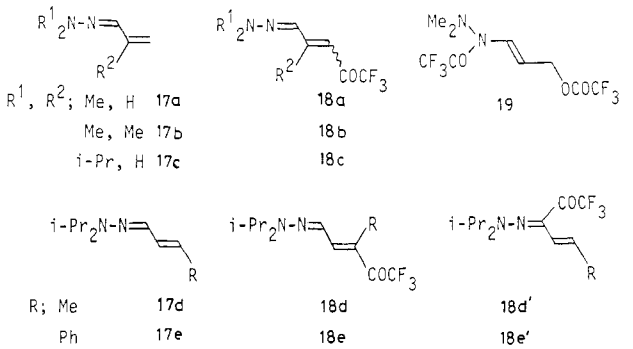


of 2,6-lutidine did not change the result at all.

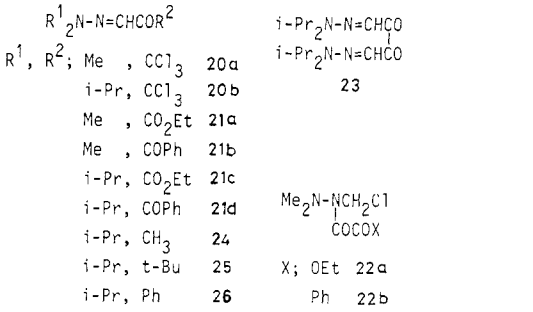
Trifluoroacetylation of Hydrazones of Aliphatic and Olefinic Aldehydes. Trifluoroacetylation of dimethylhydrazones of aliphatic aldehydes showed considerably different behavior from those observed for dimethylhydrazones of aromatic aldehydes and formaldehyde. Toward TFAA **3c** showed remarkable resistance. For instance, dimethylhydrazones of acetaldehyde **15a** and propionaldehyde **15b** did not react with 10 equiv of TFAA, even after 50 h. This seemed very strange, because even **4a**, where the strongly electron-withdrawing group $COCF_3$ is present in place of alkyl groups in **3c**, can react much more easily with TFAA at its azomethine carbon. When the reactions of **15a** and **15b** with TFAA were carried out at 80 °C in sealed tubes, there formed unexpected *N*-acyl enamines **16a** and **16b** in good yields, and no **4c** was obtained. These facts mean that N-acylation, which proceeded concurrently in the cases of **3a** and **3b**, occurred preferentially in **15a** and **15b**, so that competitive C-acylation (trifluoroacetylation at azomethine carbon) was inhibited completely. As is shown in Scheme III, **15′**, generated by N-acylation of **15**, even if existing during the reaction, would easily return to **15** on workup, or under more enhanced conditions it would be deprotonated to form **16**. Steric hindrance by the alkyl group toward C-acylation and increased electron density on the azomethine nitrogen induced by the alkyl group would also be responsible for it. In such a case introduction of bulky alkyl groups on the adjacent nitrogen is also effective to suppress this undesirable N-attack sterically. For instance, diisopropylhydrazones of acetaldehyde **15c** and propionaldehyde **15d** were readily converted to the corresponding C-acylated hydrazones **16c** and **16d**, respectively, at 0 °C. Even the benzyl derivative **15e** was easily converted to **16e** in high yield.



We then studied trifluoroacetylation of hydrazones of α,β-unsaturated aldehydes **17a–c**, where olefinic portions are R in **3c**. Interestingly behavior of **17a** and **17b** toward TFAA is quite different from that of saturated system (**15a** and **15b**). The reaction of **17a** and **17b** with TFAA is very fast and completed within a few minutes at 0 °C. However, the trifluoroacetylation in these cases occurred preferentially at the terminal olefinic carbon to afford **18a** and **18b** and not at the azomethine carbon. In the absence of pyridine[13] the reaction of **17a** in CH_2Cl_2[14] gave conjugate addition product **19** together with **18a** (2:3). With the use of pyridine as solvent, **17a** was selectively converted to **18a** and the yield was much improved. Pure **18a** is yellow and crystalline, and its longest absorption maximum appears at 392 nm (ϵ_{max} 2.52 × 10^4 in MeOH). The reaction of **17b** in CH_2Cl_2 gave **18b** as a ca. 1:2 mixture of *E* and *Z* isomers without any formation of an adduct such as a **19**. The methyl group attached to the olefinic part in **18b** probably sterically prevents N-attack of the reagent. The steric effect of the two *N*-isopropyl groups is also remarkable in these conjugate systems. For instance, **17c** was selectively and cleanly converted to **18c**. Vicinal coupling constants of the olefinic protons in **18a** (14.4 Hz) and in **18c** (15.0 Hz) revealed that these two compounds are both *E* isomers. We also examined trifluoroacetylation of diisopropylhydrazones of crotonaldehyde (**17d**) and cinnamaldehyde (**17e**). In the former case, **18d′** was obtained as a major product together with a small amount of **18d**, and in the latter case **18e′** was obtained as a sole product. Terminal methyl or phenyl groups in these two substrates sterically hindered conjugative attack of the reagent at the terminal olefinic carbon and hence favored the reaction at azomethine carbon to give **18d′** or **18e′**.



Reactions of Formaldehyde Dialkylhydrazone with Some Other Acylating Reagents. In order to ascertain the scope and limitation of the present type of electrophilic substitution reactions at olefinic carbons, we examined the reactions of formaldehyde dialkylhydrazones with several other acylating agents, including trichloroacetyl chloride, ethyl chloroglyoxylate, acetyl chloride, benzoyl chloride, and so on. As is shown in Table III, trichloroacetylation of **3a** and **8a** with trichloroacetyl chloride occurred successfully in both cases, and corresponding products **20a** and **20b**, respectively, were obtained in good yields. In the



case of **3a** no adduct corresponding to **7a** was observed in the crude products. Ethyl chloroglyoxylate and phenyl-

(13) Use of 2,6-lutidine decreased the yield of **18a**.
(14) Use of $CHCl_3$ as solvent increased the ratio of **19**/**18a** and in CCl_4 all **17a** was converted to **19**.

Table III. Reaction of 3a and 8a with Several Acylating Agents

run	substrate[a]	reagent, equiv	base,[b] equiv	$CHCl_3$, mL	time,[c] h	products	yield, %
1	**3a**	CCl_3COCl, 2	L, 2	9	3	**20a**	78
2	**8a**	CCl_3COCl, 2	L, 2	8	3	**20b**	76
3	**3a**	EtOCOCOCl, 2	L, 2	2	1	**21a, 22a**	(15/85)[d]
4		EtOCOCOCl, 2	D, 2	2	1	**21a, 22a**	(95/5)[d]
5		PhCOCOCl, 2	D, 2	2	1	**21b, 22b**	(90/10)[d]
6	**8a**	EtOCOCOCl, 1.5	L, 1.5	4	1	**21c**	75
7		PhCOCOCl, 1.5	L, 1.5	4	1	**21d**	67
8		ClCOCOCl, 0.5	L, 1.5	4	1	**23**	66
9		AcCl, 4	A, 1.2	8	3	**24**	52
10		*t*-BuCOCl, 8	A, 4	8	48	**25**	55
11		PhCOCl, 1.2	A, 1.2	8	3	**26**	46

[a] In each case 2 mmol of substrate was used. [b] L, 2,6-lutidine. D, Dabco. A, dimethylethylamine. [c] Reactions were carried out at 25 °C. [d] Product ratios (%) calculated on the basis of ^1H NMR spectra of crude products.

glyoxylyl chloride reacted with **3a** easily and the expected products **21a** and **21b**, respectively, were formed in satisfactory yields, although small amounts of addition products (**22a** and **22b**[15]) were produced. After simple column chromatography, **21a** and **21b** were easily isolated. The ratio of **21a** to **22a** varied drastically when the base was changed from 2,6-lutidine (run 3) to Dabco (run 4). Reactions of these reagents with **8a** gave **21c** and **21d**, respectively, in high yield. Oxalyl chloride reacted with twice molar amounts of **8a** to give **23**. The reaction of **3a** with acetyl chloride, pivaloyl chloride, and benzoyl chloride did not give satisfactory results. On the contrary these acylating reagents reacted with **8a** as expected and gave corresponding products **24**, **25**, and **26** in moderate yields, where dimethylethylamine was the best among several bases tested and gave the best yields. Thus **8a** is the most suitable substrate for the present acylation and is expected to react with a variety of other acylating reagents to afford corresponding products.

Conclusion

On treatment with TFAA, electrophilic substitution was found to proceed quite easily at the azomethine carbon of formaldehyde dialkylhydrazones. Trifluoroacetylation at the azomethine carbon of aliphatic aldehyde diisopropylhydrazones was also successfully performed. Trifluoroacetylation of dialkylhydrazones of α,β-unsaturated aldehydes occurred at the terminal carbon of the conjugate system and provides a new synthetic method for difunctionalized olefins. Even bistrifluoroacetylation of formaldehyde dialkylhydrazones is possible and the dimethylhydrazone was found to be converted into pyrazoles and oxadiazines bearing CF_3 groups. These heterocycles are expected to have specific biological activities.[16] The acylation can be extended to use of several other acylating reagents and has a wide potential utility in organic synthesis.

Experimental Section

All ^1H NMR spectra were recorded at 60 MHz on a JEOL PMX 60 SI spectrometer. ^{13}C NMR spectra were measured in $CDCl_3$ with a JEOL FX90 Q spectrometer with TMS as an internal standard. IR spectra were obtained on a Hitachi Model G3 spectrophotometer. UV–vis spectra were taken with a Hitachi Model 200-18 spectrophotometer.

Final purification of all products for microanalysis was done by Kugelrohr distillation or recrystallization.

Preparation of Hydrazones. Hydrazones **3a**, **15a**, and **15b** were prepared in the manner previously reported.[9]

Formaldehyde Diisopropylhydrazone (8a). To a mixture of *N,N*-diisopropylhydrazine[17] (41.4 mmol, 4.8 g) and AcOH (32 mmol, 1.92 g) in water (28 mL) was added finely powdered 80% paraformaldehyde (50 mmol, 1.875 g). After the mixture was stirred for 1 h, 30% aqueous NaOH was added until the solution turned strongly alkaline. The solution was extracted three times with ether (30 mL × 3) and the combined ethereal solution was dried over $MgSO_4$. Evaporation of the solvent afforded a pale yellow oil, which was purified by Kugelrohr distillation to give **8a** in 67% (3.55 g) yield: ^1H NMR ($CDCl_3$) δ 5.65–6.35 (AB q, J = 12 Hz, 2 H, CH_2), 3.70 (hept, J = 6 Hz, 2 H, CH), 1.1 (d, 12 H, CH_3).

Formaldehyde *tert*-Butylmethylhydrazone (8b). To a mixture of *tert*-butylhydrazone hydrochloride (60 mmol, 7.477 g) and sodium acetate (60 mmol, 4.923 g) in water (20 mL) was added finely powdered 80% paraformaldehyde (70 mmol, 2.625 g). The whole mixture was stirred for 1 h and poured onto 2 N NaOH (35 mL). The hydrazone was extracted three times with ether (30 mL × 3), and the combined ethereal layer was dried over $MgSO_4$. After removal of ether, the residual yellow oil was fractionated by Kugelrohr distillation (oven temperature 105 °C (130 Torr)). The formaldehyde *tert*-butylhydrazone (36.19 mmol, 3.623 g) thus obtained was dissolved in ether (20 mL) and then K_2CO_3 (39.34 mmol, 5.437 g) and iodomethane (282.6 mmol, 40.13 g) were added. After being stirred for 3 days, the mixture was poured onto water and the hydrazone was extracted three times with ether (30 mL × 3). The combined ethereal layer was dried over anhydrous K_2CO_3 and further with LiH. After removal of ether, the residual yellow oil was purified by Kugelrohr distillation (oven temperature 100 °C (90 Torr)) to afford **8b** in 48% (3.286 g) yield on the basis of *tert*-butylhydrazine hydrochloride: ^1H NMR (CCl_4) δ 5.88 (s, 2 H, CH_2), 2.52 (s, 3 H, NCH_3), 1.26 (s, 9 H, *t*-Bu).

Formaldehyde Methylphenylhydrazone (8c). To a solution of *N*-methyl-*N*-phenylhydrazine (50 mmol, 6.1 g) in benzene (50 mL) was added 80% paraformaldehyde (55 mmol, 2.063 g). After being stirred for 24 h, the mixture was washed with 0.1 N HCl, twice with water, and finally with aqueous Na_2CO_3. The organic layer was dried ($MgSO_4$) and removal of benzene gave a brown oil, which was purified by Kugelrohr distillation (oven temperature 75 °C (1.5 Torr)) to afford **8c** in 77% (5.159 g) yield: ^1H NMR ($CDCl_3$) δ 6.50–7.30 (m, 5 H, Ph), 5.88–6.52 (AB q, J = 13 Hz, 2 H, CH_2), 3.15 (s, 3 H, CH_3).

Formaldehyde Diphenylhydrazone (8d). To a mixture of *N,N*-diphenylhydrazine hydrochloride (10 mmol, 2.2 g) and 35% aqueous formaldehyde (11 mmol, 943 mg) was added a solution of AcONa (10 mmol, 821 mg) in water (5 mL). After being stirred for 30 min, the mixture was poured onto 1 N NaOH (50 mL). The whole mixture was well shaken and insoluble materials were filtered off. The filtrate was extracted with ether (50 mL) and the ethereal layer was dried over $MgSO_4$. Removal of the solvent followed by Kugelrohr distillation (oven temperature 150 °C (2 Torr)) of the residue afforded **8d** in 65% (1.274 g) yield as colorless oil: ^1H NMR (CCl_4) δ 6.77–7.43 (m, 10 H, Ph), 5.96 (s, 2 H, CH_2).

Aliphatic Aldehyde Diisopropylhydrazone (15c and 15d). To a solution of acetaldehyde or propionaldehyde (15 mmol) in

(15) These compounds are relatively labile and could not be isolated. ^1H NMR spectra suggest the structures of **22a** and **22b**.

(16) Reviews: Filler, R. In *Organofluorine Chemicals and Their Industrial Applications*; Banks, R. E., Ed.; Ellis Horwood: London, 1979.

(17) Lunn, G.; Sansone, E. B.; Keefer, L. K. *J. Org. Chem.* **1984**, *49*, 3470.

pentane (5 mL) was added *N,N*-diisopropylhydrazine (15 mmol, 1.74 g) and the mixture was stirred for 1 h. After pentane (10 mL) was added the mixture was washed with brine and dried over LiH. Removal of pentane and Kugelrohr distillation of the residue afforded **15c** and **15d** in 86% (1.832 g) and 93% (2.176 g) yields, respectively. **15c**: oven temperature 120 °C (33 Torr); ^{1}H NMR (CCl_4) δ 6.57 (q, J = 5 Hz, 1 H, CH), 3.45 (hept, J = 6 Hz, 2 H, NCH), 1.74 (d, 3 H, CH_3), 1.06 (d, 12 H, NCHCH_3). **15d**: oven temperature 120 °C (10 Torr); ^{1}H NMR (CCl_4) δ 6.59 (t, J = 5 Hz, 1 H, CH), 3.51 (hept, J = 6 Hz, 2 H, NCH), 2.19 (m, 2 H, CH_2), 1.03 (d and t, 15 H, CH_3).

Phenylacetaldehyde Diisopropylhydrazone (15e). To a solution of phenylacetaldehyde (15 mmol, 1.8 g) in benzene (3 mL) was added *N,N*-diisopropylhydrazine (16.5 mmol, 1.914 g). After stirring for 3 h, benzene (50 mL) was added, and the mixture was washed with water. The organic layer was dried ($MgSO_4$), benzene was removed, and the residual oil was fractionated by Kugelrohr distillation (oven temperature 100 °C (2 Torr)) to afford **15e** in 92% (3.008 g) yield: ^{1}H NMR (CCl_4) δ 6.91 (s, 5 H, Ph), 6.38 (t, J = 5 Hz, 1 H, CH), 3.66–3.93 (hept and d, 4 H, NCH and CH_2), 1.06 (d, J = 6 Hz, 12 H, CH_3).

Conjugated Hydrazones (17a, 17b, 17c, 17d, and 17e). General Procedure. To a solution of hydrazine (40 mmol) in CH_2Cl_2 (40 mL) was added dropwise AcOH (40 mmol, 2.4 g) with continuous stirring. After cooling the mixture in an ice bath, aldehyde (40 mmol) was added and the whole mixture was stirred for 10 min without further cooling. After CH_2Cl_2 (40 mL) was added, the mixture was washed thoroughly with aqueous Na_2CO_3 and dried over $MgSO_4$. Removal of the solvent and fractionation of the residual material by Kugelrohr distillation afforded **17a–e**. **17a** (3.88 g, 99%): oven temperature 165 °C (150 Torr); ^{1}H NMR (CCl_4) δ 6.74 (d, J = 8.4 Hz, 1 H, N=CH), 6.29 (m, 1 H, CH=CH_2), 4.85–5.30 (m, 2 H, =CH_2), 2.80 (s, 6 H, CH_3). **17b** (4.12 g, 92%): oven temperature 150 °C (140 Torr); ^{1}H NMR (CCl_4) δ 6.88 (s, 1 H, CH), 4.95 (m, 2 H, CH_2), 2.79 (s, 6 H, NCH_3), 1.87 (s, 3 H, CH_3). **17c** (5.30 g, 86%): oven temperature 115 °C (60 Torr); ^{1}H NMR (CCl_4) δ 6.88 (d, J = 7 Hz, 1 H, N=CH), 6.46 (m, 1 H, CH=CH_2), 4.77–5.16 (m, 2 H, CH_2), 3.74 (hept, J = 6.6 Hz, 2 H, CH), 1.12 (d, 12 H, CH_3). **17d** (6.05 g, 90%): oven temperature 100 °C (8 Torr); ^{1}H NMR (CCl_4) δ 6.81 (d, J = 7.8 Hz, 1 H, N=CH), 5.11–6.27 (m, 2 H, CH=), 3.72 (hept, J = 6.0 Hz, 2 H, CH), 1.76 (d, J = 5.0 Hz, 3 H, =CHCH_3), 1.09 (d, 12 H, CH_3). **17e** (8.56 g, 93%): oven temperature 185 °C (3 Torr); ^{1}H NMR (CCl_4) δ 6.09–7.24 (m, 8 H, =CH, Ar), 3.73 (hept, J = 6.4 Hz, 2 H, CH), 1.13 (d, 12 H, CH_3).

Trifluoroacetylation of Formaldehyde Hydrazones 3a, 8a, 8b, 8c, and 8d (Refer to Table I). General Procedure. To an ice-cooled mixture of hydrazone (2 mmol) and amine (4–12 mmol) in dry $CHCl_3$ ($^4/_5$ of the total volume) was added dropwise a solution of TFAA (3–12 mmol) in dry $CHCl_3$ ($^1/_5$ of the total volume) with continuous stirring (in the case of run 6 this process was carried out at −40 °C). After stirring under the conditions shown in Table I, CH_2Cl_2 (50 mL) was added and the whole mixture was washed with 0.1 N HCl, then with water, and finally with aqueous Na_2CO_3. The mixture was dried over Na_2SO_4 and the solvent was removed. In the cases of runs 1–4, 7, and 8 was obtained a mixture of **4a**[9] and **7a**[9]: 71/29, 323 mg (run 1); 88/12, 320 mg (run 2); 90/10, 324 mg (run 3); 92/8, 284 mg (run 4); 83/17, 322 mg (run 7); 91/9, 303 mg (run 8). In the cases of runs 5 and 6, Kugelrohr distillation of the crude materials afforded 276 mg (82%) and 222 mg (66%), respectively, of **4a** as yellow oil. In the cases of runs 9 and 10, Kugelrohr distillation of the crude materials gave 426 mg (95%) of **9a** and 407 mg (97%) of **9b**, respectively. In the case of run 11, the crude material was recrystallized from *n*-hexane to afford 405 mg (88%) of **9c**. In the case of run 12, the crude material was fractionated by silica gel column chromatography. The eluent with hexane/benzene (1/4) gave 299 mg (51%) of **9d** and that with benzene afforded 149 mg (27%) of *N'*-(trifluoroacetyl)-*N,N*-diphenylhydrazide[18] resulting from hydrolysis of **7b**.

Bistrifluoroacetylation of Formaldehyde Dialkylhydrazones. Trifluoroacetylation of 9a. To a mixture of **9a** (0.45 mmol, 100 mg) and 2,6-lutidine (1.35 mmol, 145 mg) in dry $CHCl_3$ (0.5 mL) was added dropwise TFAA (3.6 mmol, 756 mg). The mixture was stirred for 3 h and then CH_2Cl_2 (20 mL) was added. The whole mixture was washed with 0.1 N HCl, with water, and finally with aqueous Na_2CO_3. After drying the mixture over Na_2SO_4, the solvent was removed. Kugelrohr distillation of the residue afforded 112 mg (78%) of crystalline **10a**.

Bistrifluoroacetylation of 3a (Refer to Table II). Reaction and workup procedures were quite similar to those for trifluoroacetylation of **3a** except for the use of TFAA in excess. Crude material (2.945 g) was fractionated by silica gel column chromatography and gave 804 mg (15%) of **11a** with *n*-hexane/benzene (5/1), 22 mg (0.4%) of **10b** with *n*-hexane/benzene (4/1), 344 mg (7%) of **12a** with *n*-hexane/benzene (2/3), and 739 mg (22%) of **4a** with *n*-hexane/benzene (1/4). No adduct **7a** was recovered.

Trifluoroacetylation of 4a (Refer to Table II). Reaction and workup procedures were quite similar to those for trifluoroacetylation of **3a**. Crude materials were analyzed by means of ^{1}H NMR spectroscopy. In the cases of runs 2 and 7 were obtained 186 mg of a mixture of **4a**, **11a**, and **12a** (42/24/34) and 498 mg of the same mixture (33/35/32), respectively. In runs 3 and 5 were obtained 219 mg of a mixture of **11a** and **12a** (50/50) and 512 mg of the mixture (40/60), respectively. In the cases of runs 4 and 6 were obtained 178 mg of a mixture of **4a**, **10b**, **11a**, and **12a** (11/15/46/28) and 474 mg of the the same mixture (12/16/42/30), respectively. The crude material of run 6 was fractionated by silica gel column chromatography, from which were obtained 113 mg (21%) of **11a** with *n*-hexane/benzene (5/1), 70 mg (13%) of **10b** with *n*-hexane/benzene (4/1), 118 mg (24%) of **12a** with *n*-hexane/benzene (1/1), and 32 mg (9.5%) of **4a** with *n*-hexane/benzene (1/4). In the case of run 8 the treatment with aqueous HCl in workup was omitted and 166 mg (63%) of **11a** was obtained.

Trifluoroacetylation of 7a (Refer to Table II). Reaction and workup procedures were quite similar to those for trifluoroacetylation of **3a**, and 271 mg (96%) of **7a** was recovered.

Thermal Treatment of 4a. A solution of **4a** (1 mmol, 168 mg) in CCl_4 (30 mL) was stirred for 2 days under reflux conditions. After removal of the solvent **4a** was recovered quantitatively. The reaction of **4a** (0.8 mmol, 134 mg) under more enhanced conditions was carried out in an N_2 atmosphere in a sealed tube by heating it at 100 °C for 2 days. An unidentified tarry mixture (95 mg) was produced.

Reaction of 4a in the Presence of TFA or(and) 2,6-Lutidine. In a 5 mm i.d. NMR tube **4a** (0.5 mmol, 84 mg) was dissolved in $CDCl_3$ (0.5 mL). Then TFA or 2,6-lutidine (2 mmol) was added and reactions were monitored by ^{1}H NMR spectroscopy. After 7 days there occurred no changes in the spectra. To a mixture of **4a** (2 mmol, 336 mg) and 2,6-lutidine (4 mmol, 429 mg) in dry $CHCl_3$ (2 mL) was added dropwise TFA (4 mmol, 840 mg). After stirring for 7 days, CH_2Cl_2 (20 mL) was added and the whole mixture was washed with 0.1 N HCl, with water, and finally with aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4) and the solvent was removed. The resulting yellow oil was **4a** (302 mg, 97% recovery).

Reaction of 13b (Ar = *p*-Tol) with TFAA. Quite similar to the case of trifluoroacetylation of **3a**, **13b**[9] (1 mmol, 258 mg) was treated with TFAA (4 mmol, 840 mg) in the presence of 2,6-lutidine (2 mmol, 214 mg). Reaction was carried out in dry $CHCl_3$ (2 mL) for 6 days at 30 °C. Similar workup afforded 232 mg of an orange oil, which was **13b** containing small amounts of unidentified materials.

Conversion of 10b to 12a. Reaction and workup were quite similar to those for trifluoroacetylation of **3a**. A mixture of **10b** (0.5 mmol, 132 mg), 2,6-lutidine (1 mmol, 107 mg), and TFAA (2 mmol, 420 mg) in $CHCl_3$ (1 mL) was stirred for 2 days. The crude material was almost pure **12a** (113 mg, 92%).

Trifluoroacetylation of 9b and 9c. Reaction and workup procedures were quite similar to those for trifluoroacetylation of **9a**. For **9b** (2 mmol, 420 mg) were used TFAA (16 mmol, 3.36 g), 2,6-lutidine (6 mmol, 643 mg), and dry $CHCl_3$ (9 mL) as a solvent. Reaction for 1 h gave 350 mg of a mixture of **10c** and **12b** (13/87) and fractionation of it by preparative TLC (SiO_2/Merck 60PF) using benzene as developing solvent afforded 61

(18) This compound was identified by mixture melting points (mp 192 °C) with the authentic sample prepared from commercially available *N,N*-diphenylhydrazine hydrochloride and TFAA in the presence of pyridine.

mg (10%) of **10c** and 380 mg (66%) of **12b**. For **9c** (2 mmol, 460 mg) were used TFAA (12 mmol, 2.52 g), 2,6-lutidine (6 mmol, 643 mg), and dry $CHCl_3$ (2 mL) as a solvent. After reaction for 24 h, 202 mg of **9c** was recovered.

Trifluoroacetylation of 15a and 15b. Reaction and workup procedures were quite similar to those for trifluoroacetylation of **3a**. For **15a** and **15b** (2 mmol) were used TFAA (20 mmol, 4.2 g), 2,6-lutidine (8 mmol, 857 mg), and dry $CHCl_3$ (2 mL) as a solvent. After reaction for 50 h, 119 mg (69%) of **15a** and 148 mg (74%) of **15b** were recovered. The reaction in a sealed tube was carried out as follows. To a mixture of **15a** (2 mmol, 172 mg) and 2,6-lutidine (4 mmol, 429 mg) in dry $CHCl_3$ (5 mL) was added TFAA (8 mmol, 1.68 g) dissolved in dry $CHCl_3$ (1 mL). The mixture was stirred for 1 min, transferred into a sealed tube, and heated for 24 h at 60 °C. The contents in the sealed tube were poured onto 40 mL of 0.1 N HCl; then CH_2Cl_2 (20 mL) was added and the whole mixture was well shaken. The organic layer was separated, washed with water and then with aqueous Na_2CO_3, and dried over $MgSO_4$. Removal of the solvent and Kugelrohr distillation of the residue gave 229 mg (63%) of **16a**.

Trifluoroacetylation of 15c, 15d, and 15e. Reaction and workup procedures were quite similar to those for trifluoroacetylation of **3a**. For **15c–e** (1 mmol) were used TFAA (1.5 mmol, 315 mg), 2,6-lutidine (2 mmol, 214 mg), and dry $CHCl_3$ (2 mL) as a solvent. Reaction for 5 min at 0 °C afforded 231 mg (97%) of **16c**, 247 mg (98%) of **16d**, and 286 mg (91%) of **16e**.

Trifluoroacetylation of 17a, 17b, 17c, 17d, and 17e. Reaction and workup procedures were quite similar to those for trifluoroacetylation of **3a**. For 5 mmol of substrates were used TFAA (7.5 mmol, 1.57 g), pyridine (6 mmol, 475 mg), and dry CH_2Cl_2 (10 mL) as solvent. Reaction for 5 min at 20 °C gave 697 mg of a mixture of **18a** and **19** (57:43) from **17a**, 894 mg (86%) of **18b** (E/Z = 9/11) from **17b**, 988 mg (79%) of **18c** from **17c**, 1.254 g of a mixture of **18d** and **18d'** (1:4) from **17d**, and 1.516 g (93%) of **18e'** from **17e**. The mixture of **18a** and **19** was fractionated by silica gel column chromatography. With benzene 132 mg (9%) of **19** and with benzene/CH_2Cl_2 (5/1) 302 mg (31%) of **18a** were eluted. The mixture of **18d** and **18d'** was fractionated by preparative TLC (SiO_2/Merck 60PF) using benzene/CH_2Cl_2 (1/1) as developing solvent to afford 226 mg (17%) of **18d** and 922 mg (70%) of **18d'**. Trifluoroacetylation of **17a** using pyridine as a solvent was carried out as follows. To ice-cold **17a** (5 mmol, 490 mg) in pyridine (2 mL) was added dropwise TFAA (7.5 mmol, 1.57 g). The whole mixture was stirred for 5 min at 20 °C and CH_2Cl_2 (20 mL) was added to this. The mixture was washed with water and dried over $MgSO_4$. Removal of pyridine under vacuum followed by Kugelrohr distillation of the residue gave 485 mg (50%) of **18a**.

Acylation of Formaldehyde Dialkylhydrazone with Some Other Acylating Reagents (Refer to Table III). General Procedure. To a mixture of substrate (2 mmol) and amine in dry $CHCl_3$ (the total volume minus 1 mL) was added the acylating reagent dissolved in dry $CHCl_3$ (1 mL) dropwise, and the mixture was stirred for 1–48 h at 25 °C. Runs 1–8: The reaction mixture was poured onto 0.5 N HCl (ca. 100 mL) and stirred for 10 min. To this was added CH_2Cl_2 (50 mL) and the organic layer was separated and dried over Na_2SO_4. After removal of the solvent, Kugelrohr distillation of the residue gave 339 mg (78%) of **20a** (run 1). Recrystallization of the residue afforded 416 mg (76%) of **20b** (run 2) and 205 mg (66%) of **23** (run 8). In the cases of runs 3 and 4, 387 mg of the crude mixture (**21a**/**22a** = 15/85) and 350 mg of **21a**/**22a** (95/5) were obtained, respectively. The latter was fractionated by silica gel column chromatography, from which 236 mg (69%) of **21a** was eluted with benzene/AcOEt (7/3). In the case of run 5, 392 mg of a mixture (**21b**/**22b** = 90/10) was obtained. This was fractionated by silica gel column chromatography and 237 mg (58%) of **21b** was obtained with CH_2Cl_2/AcOEt (4/1). In the cases of runs 6 and 7, silica gel chromatography of the crude materials gave 342 mg (75%) of **21c** with benzene/CH_2Cl_2 (1/9) and 348 mg (67%) of **21d** with benzene/CH_2Cl_2 (3/7), respectively. Runs 9–11: After MeOH (1 mL) was added (in the cases of runs 9 and 10), the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with 1 N NaOH, and dried over Na_2SO_4. Removal of the solvent afforded crude products, which were purified by silica gel column chromatography. In the cases of runs 9 and 10, the eluent with CH_2Cl_2 gave 177 mg (52%) of **24** and 233 mg (55%) of **25**, respectively. In the case of run 11 elution with CH_2Cl_2/AcOEt (9/1) afforded 213 mg (46%) of **26**.

Physical and Spectroscopic Data for 7b–26.[19] **7b**: ^1H NMR ($CDCl_3$) δ 6.80–7.50 (m, 10 H, Ph), 5.79 (s, 2 H, CH_2). **7b'**: colorless crystals; mp 186 °C (recrystallized from cyclohexane); IR 3280 (s), 1720 (s), 1580 (s), 1485 (s), 1160 (s), 669 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.2 (br, 1 H, NH), 6.90–7.40 (m, 10 H, Ph). **9a**: pale yellow oil; oven temperature 100 °C (2 Torr); IR 2900 (m), 1670 (s), 1510 (s), 1320 (m), 1180 (m), 1120 (s), 1000 (m), 830 (m), 670 (m), 600 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (s, 1 H, =CH), 3.95 (hept, J = 6 Hz, 2 H, NCH), 1.20 (d, 12 H, CH_3). **9b**: yellow oil; oven temperature 110 °C (2 Torr); IR 2860 (m), 1660 (s), 1500 (S), 1320 (s), 1170 (s), 1120 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (s, 1 H, =CH), 2.93 (s, 3 H, CH_3), 1.37 (s, 9 H, t-Bu). **9c**: yellow crystals; mp 65 °C (recrystallized from n-hexane); IR 1685 (s), 1590 (m), 1530 (s), 1490 (s), 1330 (s), 1250 (m), 1180 (s), 1140 (s), 750 (s), 680 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97–7.40 (m, 5 H, Ph), 6.95 (s, 1 H, =CH), 3.45 (s, 3 H, CH_3). **9d**: yellow crystals; mp 94 °C (recrystallized from cyclohexane); IR 1672 (m), 1480 (s), 1306 (m), 1235 (m), 1104 (s), 747 (m), 679 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90–7.60 (m, 10 H, Ph), 6.50 (q, $^4J_{H-F}$ = 2 Hz, 1 H, CH). **10a**: pale orange crystals; mp 107 °C; oven temperature 150 °C (1 Torr); IR 1722 (m), 1652 (s), 1503 (s), 1347 (m), 1179 (s), 1144 (s), 1096 (s), 960 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.50–4.10 (br, 2 H, CH), 1.28 (d, J = 7 Hz, 12 H, CH_3). **10b**: yellow oil; oven temperature 95 °C (3 Torr); IR 1650 (s), 1300 (s), 1150 (s), 1000 (s), 910 (m), 730 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (s, br, 6 H, CH_3). **10c**: yellow oil; ^1H NMR (CCl_4) δ 2.84 (s, 3 H, NCH_3), 1.46 (s, 9 H, t-Bu). **11a**: colorless oil; oven temperature 75 °C (2.5 Torr); IR 1720 (s), 1400 (s), 1350 (s), 1200 (s), 1170 (m), 950 (m), 900 (m), 830 (m), 750 (m), 650 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10 (s, 1 H, CH=), 4.70, 4.80 (AB q, J = 10 Hz, 2 H, CH_2), 2.80 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 154.5 ($^2J_{C-F}$ = 38 Hz, CF_3CO), 133.4 ($^2J_{C-F}$ = 39 Hz, —$(CF_3)C$=), 119.3 ($^1J_{C-F}$ = 271 Hz, —$(CF_3)C$=), 115.9 ($^1J_{C-F}$ = 287 Hz, $COCF_3$), 104.1 ($^1J_{C-H}$ = 193 Hz, NCH=), 84.0 ($^1J_{C-H}$ = 166 Hz, CH_2), 40.9 ($^1J_{C-H}$ = 138 Hz, CH_3); MS, m/e (M^+) 264 (100).[20] **12a**: colorless crystals; mp 83 °C (recrystallized from cyclohexane); IR 1710 (s), 1260 (s), 1200 (m), 1150 (s), 910 (m), 730 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (s, 1 H, CH), 4.05 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.8 ($^2J_{C-F}$ = 38 Hz, CF_3CO), 140.9 (N=C), 132.9 ($^1J_{C-H}$ = 195 Hz, $^3J_{C-F}$ = 4.6 Hz, NCH=), 121.1 ($^1J_{C-F}$ = 267 Hz, —(CF_3)C=), 117.1 ($^2J_{C-F}$ = 40 Hz, —$(CF_3)C$=), 116.1 ($^1J_{C-F}$ = 290 Hz, CF_3CO), 40.5 ($^1J_{C-H}$ = 142 Hz, CH_3);[21] MS, m/e (M^+) 246 (1.9).[20] **12b**: colorless crystals; mp 43 °C; oven temperature 75 °C (2 Torr); IR 1725 (s), 1250 (s), 1200 (s), 1140 (s), 1070 (m), 910 (s) cm^{-1}; ^1H NMR (CCl_4) δ 7.73 (s, 1 H, CH), 1.67 (s, 9 H, t-Bu). **16a**: orange oil; IR 1712 (s), 1637 (w), 1595 (w), 1390 (w), 1335 (w), 1160 (s), 1046 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.53 (q, J = 16 Hz, 9.4 Hz, 1 H, CH=), 5.20, 4.90 (d, 2 H, $=CH_2$), 2.75 (s, 6 H, NCH_3). **16c**: colorless crystals; mp 65 °C (recrystallized from EtOH/H_2O); IR 2980 (m), 1660 (s), 1520 (s), 1335 (m), 1270 (m), 1210 (m), 1150 (s), 1015 (s), 900 (m), 700 (m), cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (m, 2 H, NCH), 2.25 (s, 3 H, CH_3), 1.25 (d, J = 6.5 Hz, 12 H, $NCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 178.1 ($^2J_{C-F}$ = 29 Hz, CO), 126.4 (N=C), 118.5 ($^1J_{C-F}$ = 291 Hz, CF_3), 52.4 (CH), 21.6 ($CHCH_3$), 13.5 (CH_3). **16d**: pale yellow crystals; mp 78 °C (recrystallized from EtOH/H_2O); IR 1670 (s), 1528 (s), 1348 (s), 1209 (s), 1175 (s), 1150 (s), 1053 (s) cm^{-1}; ^1H NMR (CCl_4) δ 4.07 (hept, J = 6 Hz, 2 H, CH), 2.53 (q, J = 7 Hz, 2 H, CH_2), 1.26, 1.05 (d, t, 15 H, CH_3). **16e**: pale yellow crystals; mp 47 °C (recrystallized from n-heptane); IR 1668 (s), 1520 (s), 1355 (s), 1287 (s), 1229 (s), 1150 (s), 1103 (m), 1017 (m), 972 (s), 707 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.77–7.33 (m, 5 H, Ph), 4.03 (m, 2 H, CH), 3.95 (s, 2 H, CH_2), 1.12 (d, J = 6.5 Hz, 12 H, CH_3). **18a**:

(19) Satisfactory microanalytical data were reported for all new compounds isolated.

(20) We thank Dr. Toshiro Harada of Kyoto Institute of Technology for measurement of mass spectra.

(21) Observed ^{13}C–H coupling constants at pyrazole ring C^5 (195 Hz) and ^{13}C chemical shift of NMe (40.5 ppm) of **12a** are characteristic to such types of pyrazoles but deviate from those expected for imidazoles. In addition all ^{13}C chemical shifts of **12a** are very reasonable compared to those of 4-(trifluoroacetyl)-3-(trifluoromethyl)-1-methylpyrazole, which was prepared independently and will be published in a forthcoming papers.

yellow crystals; mp 42 °C; oven temperature 120 °C (1 torr); IR 1674 (m), 1585 (s), 1512 (s), 1380 (s), 1324 (m), 1256 (m), 1232 (s), 1182 (s), 1124 (s), 1061 (s) cm^{-1}; ^1H NMR (CCl_4) δ 7.53 (q, 1 H, CH=C), 6.76 (d, J = 9.0 Hz, 1 H, N=CH), 6.19 (d, J = 14.4 Hz, 1 H, =CHCO), 3.13 (s, 6 H, CH_3); UV (MeOH) λ_{max} (ϵ_{max}) 230 (3590), 285 (6470), 392 (25 200) nm. **18b**: yellow crystals; mp 26 °C (E/Z = 11/24); oven temperature 150 °C (3.5 Torr); IR 1675 (s), 1195 (s), 1130 (m), 830 (m), 795 (m) cm^{-1}; ^1H NMR (CCl_4) δ 8.11 (s, N=CH of Z isomer), 6.67 (s, N=CH of E isomer), 6.16 (s, =CHCO of E isomer), 5.98 (s, =CHCO of Z isomer), 3.16 (s, NCH_3 of Z isomer), 3.08 (s, NCH_3 of E isomer), 2.39 (s, CH_3 of E isomer), 2.15 (s, CH_3 of Z isomer). **18c**: yellow oil; oven temperature 150 °C (3 Torr); IR 1665 (s), 1565 (s), 1495 (s), 1400 (m), 1370 (m), 1313 (m), 1245 (s), 1185 (m), 1130 (s), 1050 (s), 837 (m), 715 (s) cm^{-1}; ^1H NMR (CCl_4) δ 7.61 (q, 1 H, CHC*H*=), 7.01 (d, J = 9.6 Hz, 1 H, N=CH), 6.15 (d, J = 15 Hz, 1 H, =CHCO), 3.96 (hept, J = 6.6 Hz, 2 H, CH), 1.24 (d, 12 H, CH_3). **18d**: yellow crystals; mp 109 °C (recrystallized from $MeOH/H_2O$); IR 1655 (s), 1583 (s), 1505 (s), 1350 (m), 1215 (s), 1195 (s), 1182 (s), 1152 (s), 1130 (s), 1092 (m), 1017 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (d, J = 9.0 Hz, 1 H, CH=C), 7.10 (d, 1 H, N=CH), 3.99 (hept, J = 6.6 Hz, 2 H, CH), 1.96 (s, 3 H, =CCH_3), 1.26 (d, 12 H, CH_3). **18d′**: colorless crystals; mp 76 °C (recrystallized from n-heptane); IR 1680 (s), 1508 (s), 1335 (m), 1205 (s), 1175 (s), 1145 (m), 971 (m) cm^{-1}; ^1H NMR (CCl_4) δ 5.99 (m, 1 H, =C*H*CH_3), 5.80 (d, J = 14.8 Hz, 1 H, CH=C), 4.25 (hept, J = 6.6 Hz, 2 H, CH), 1.86 (d, J = 5.4 Hz, 3 H, =CHC*H*$_3$), 1.25 (d, 12 H, CH_3). **18e′**: orange crystals; mp 85 °C (recrystallized from n-hexane); IR 1674 (s), 1516 (s), 1345 (m), 1278 (m), 1214 (m), 1162 (s), 1097 (m), 963 (m) cm^{-1}; ^1H NMR (CCl_4) δ 7.18 (m, 5 H, Ph), 7.02 (d, J = 16.6 Hz, 1 H, =C*H*Ph), 6.37 (d, 1 H, CH=C), 4.31 (hept, J = 6.6 Hz, 2 H, CH), 1.30 (d, 12 H, CH_3). **19**: pale yellow oil; oven temperature 150 °C (1 Torr); IR 1776 (s), 1705 (s), 1190 (s), 1142 (s) cm^{-1}; ^1H NMR (CCl_4) δ 6.67 (d, J = 14.4 Hz, 1H, NCH=), 6.14 (q, 1 H, =CH), 4.79 (d, J = 6.6 Hz, 2 H, CH_2), 2.77 (s, 6 H, CH_3). **20a**: pale yellow oil; oven temperature 140 °C (3 Torr); IR 1670 (s), 1500 (s), 1380 (s), 1130 (m), 1070 (s), 830 (s), 790 (s), 710 (s), 650 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (s, br, 1 H, CH), 3.28 (s, 6 H, CH_3). **20b**: yellow crystals; mp 93 °C (recrystallized from n-hexane/cyclohexane); IR 2950 (s), 1645 (s), 1500 (s), 1360 (m), 1225 (s), 1145 (m), 1085 (m), 1010 (m), 880 (m), 830 (m), 800 (s), 735 (m), 645 (s) cm^{-1}; ^1H NMR (CCl_4) δ 6.98 (s, 1 H, =CH), 4.07 (hept, J = 6.6 Hz, 2 H, CH), 1.29 (d, 12 H, CH_3). **21a**: brown oil; oven temperature 207 °C (2 Torr); IR 2950 (m), 1730 (s), 1640 (s), 1515 (s), 1300 (s), 1150 (s), 1090 (m), 1010 (m), 830 (m), 665 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (s, 1 H, =CH), 4.25 (q, J = 7 Hz, 2 H, CH_2), 3.20 (s, 6 H, NCH_3), 1.35 (t, 3 H, CH_3). **21b**: yellow crystals; mp 83 °C (recrystallized from n-hexane/benzene); IR 1660 (s), 1630 (s), 1500 (s), 1410 (s), 1310 (s), 1290 (s), 1190 (s), 1090 (s), 960 (m), 840 (m), 630 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.90 (m, 5 H, Ph), 6.70 (s, 1 H, CH), 3.10 (s, 6 H, CH_3). **21c**: orange oil; oven temperature 120 °C (2 Torr); IR 2915 (s), 1730 (m), 1645 (s), 1495 (s), 1130 (s) cm^{-1}; ^1H NMR (CCl_4) δ 6.67 (s, 1 H, =CH), 3.63–4.35 (q and hept, 4 H, CH_2 and CH), 1.23, 1.33 (d, J = 6 Hz and, t, J = 8 Hz, 15 H, NCH_3 and CH_3). **21d**: colorless crystals; mp 139 °C (recrystallized from cyclohexane); IR 1677 (s), 1637 (s), 1504 (s), 1282 (m), 1243 (m), 1200 (s), 1152 (m), 963 (m), 630 (m) cm^{-1}; ^1H NMR (CCl_4) δ 7.30–7.93 (m, 5 H, Ph), 6.97 (s, 1 H, =CH), 4.00 (hept, J = 6 Hz, 2 H, CH), 1.07 (d, 12 H, CH_3). **22a** (not isolated): ^1H NMR ($CDCl_3$) δ 5.30 (s, 2 H, NCH_2), 4.25 (q, J = 7 Hz, 2 H, OCH_2), 2.65 (s, 6 H, NCH_3), 1.35 (t, 3 H, CH_3). **22b** (not isolated): ^1H NMR ($CDCl_3$) δ 7.10–7.90 (m, 5 H, Ph), 5.35 (s, 2 H, NCH_2), 2.50 (s, 6 H, NCH_3). **23**: pale yellow crystals; mp 175 °C (recrystallized from benzene); IR 2980 (m), 1650 (s), 1520 (s), 1290 (m), 1240 (m), 1130 (m), 620 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (s, 2 H, =CH), 3.85 (m, 4 H, NCH), 1.15 (d, J = 6 Hz, 24 H, CH_3). **24**: pale orange oil: oven temperature 61 °C (3 Torr); IR 2970 (m), 1645 (s), 1520 (s), 1355 (m), 1230 (s), 1140 (m), 598 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (s, 1 H, =CH), 3.80 (hept, J = 6 Hz, 2 H, NCH), 2.20 (s, 3 H, $COCH_3$), 1.20 (d, 12 H, CH_3). **25**: colorless crystals; mp 80 °C (recrystallized from pentane); IR 2900 (s), 1620 (s), 1520 (s), 1360 (m), 1290 (m), 1230 (m), 1130 (s), 1100 (m), 870 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (s, 1 H, =CH), 3.80 (hept, J = 6 Hz, 2 H, NCH), 1.30 (s, 9 H, t-Bu), 1.20 (d, 12 H, CHC*H*$_3$). **26**: yellow crystals; mp 59 °C; oven temperature 130 °C (2 Torr); IR 2587 (m), 1612 (s), 1512 (s), 1285 (s), 1235 (s), 1143 (s), 1094 (m), 1014 (m), 838 (m), 793 (m), 757 (m), 704 (m), 641 (m) cm^{-1} ; ^1H NMR (CCl_4) δ 7.20–7.97 (m, 5 H, Ph), 7.03 (s, 1 H, =CH), 3.95 (hept, J = 6 Hz, 2 H, NCH), 1.17 (d, 12 H, CH_3).

Registry No. **3a**, 2035-89-4; **4a**, 111269-38-6; **7a**, 111269-39-7; **7b**, 111999-21-4; **8a**, 39837-46-2; **8b**, 111999-12-3; **8c**, 15754-28-6; **8d**, 38392-47-1; **9a**, 111999-17-8; **9b**, 111999-18-9; **9c**, 111999-19-0; **9d**, 111999-20-3; **10a**, 111999-23-6; **10b**, 111999-24-7; **10c**, 111999-27-0; **11a**, 111999-25-8; **12a**, 111999-26-9; **12b**, 111999-28-1; **13b**, 111269-50-2; **15a**, 7422-90-4; **15b**, 7422-93-7; **15c**, 67660-50-8; **15d**, 111999-13-4; **15e**, 111999-14-5; **16a**, 111999-29-2; **16b**, 111269-37-5; **16c**, 112021-10-0; **16d**, 111999-30-5; **16e**, 111999-31-6; **17a**, 25368-52-9; **17b**, 16713-45-4; **17c**, 16713-53-4; **17d**, 111999-15-6; **17e**, 111999-16-7; **18a**, 111999-32-7; (*E*)-**18b**, 111999-34-9; (*Z*)-**18b**, 111999-35-0; **18c**, 111999-36-1; **18d**, 111999-37-2; **18d′**, 111999-38-3; **18e′**, 111999-39-4; **19**, 111999-33-8; **20a**, 111999-40-7; **20b**, 111999-41-8; **21a**, 111999-42-9; **21b**, 111999-43-0; **21c**, 111999-44-1; **21d**, 111999-45-2; **22a**, 111999-50-9; **22b**, 111999-51-0; **23**, 111999-49-6; **24**, 111999-46-3; **25**, 111999-47-4; **26**, 111999-48-5; i-Pr_2NNH_2, 921-14-2; t-BuNHNH_2·HCl, 7400-27-3; t-BuNHN=CH_2, 108199-32-2; MePhNNH_2, 618-40-6; Ph_2NNH_2, 530-47-2; MeCHO, 75-07-0; EtCHO, 123-38-6; $PhCH_2CHO$, 122-78-1; H_2C=CHCHO, 107-02-8; H_2C=C(Me)CHO, 78-85-3; MeCH=CHCHO, 4170-30-3; PhCH=CHCHO, 104-55-2; Me_2NNH_2, 30260-66-3; CCl_3COCl, 76-02-8; EtOCOCOCl, 4755-77-5; PhCOCOCl, 25726-04-9; ClCOCOCl, 79-37-8; AcCl, 75-36-5; t-BuCOCl, 3282-30-2; PhCOCl, 98-88-4; $Ph_2NNHCOCF_3$, 111999-22-5.