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Comparative Study of the Chemoselectivity and Yields of the Synthesis of *N*-Alkyl-4-(trihalomethyl)-1*H*-pyrimidin-2-ones

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This paper reports a comparative study of the chemoselectivity and yields of the synthesis of *N*-alkyl-4-(trihalomethyl)-1*H*-pyrimidin-2-ones carried out by the cyclocondensation of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones (enones) with methyl- and allylureas with the *N*-alkylation of 4-(trihalomethyl)-1*H*-pyrimidin-2-ones with methyl iodide and allyl bromide. To determine the chemoselectivity of the products obtained, all compounds were fully analyzed by ^{1}H and ^{13}C NMR and 2D HMBC spectroscopy. This study has demonstrated that the cyclocondensation reactions give better yields and furnish either N^1- or N^3-alkylated products depending on both the reaction conditions and the substituents on the enones, whereas the alkylation of pyrimidin-2-ones gives lower overall yields and either an N^1-alkylated product or a mixture of N^1- and *O*-alkylated products.

Introduction

Pyrimidines have a long history of biological activity ranging from pharmaceutical to agricultural fields. The introduction of a trifluoromethyl group into bioactive molecules often increases their therapeutic efficiency due to an increase in their lipophilicity.[1] Thus, pyrimidines bearing a trifluoromethyl group have demonstrated a variety of activities such as herbicidal,[2] insecticidal,[3] acaricidal,[4] fungicidal,[4] antitumoral,[5] and antiviral,[6] just to mention a few. Trichlorinated substituted heterocycles have been the subject of fewer studies. However, recent investigations have shown that, in some cases, trichloromethyl-containing heterocycles are more active than the corresponding trifluoromethyl-substituted analogues, for example, they have shown NTPDase inhibitory effects in synaptosomes from rat cerebral cortex,[7] antinociceptive effects in mice,[8] and hypothermic and antipyretic effects.[9]

The *N*-alkylation of pyrimidines is one way of functionalizing the pyrimidine ring to achieve important physical and bioactive properties. For example, *N*-alkylated nucleic acid bases are widely known for being the most effective antiviral[10] and antitumoral agents,[11] as well as for exerting antiinflammatory[12] and herbicidal activity.[13] In addition, *N*-alkylated pyrimidines, obtained by alkylating agents such as diazoalkanes,[14] alkyl halides[15] and alkyl sulfates, among others,[16] are important compounds for mutagenic and carcinogenic studies in living systems.

Very few studies have reported on the synthesis of *N*-alkylated pyrimidin-2-ones by cyclocondensation reactions using nonsymmetric ureas. Probably the main reason for this is that ureas are weak nucleophiles, and they do not react very well with 1,3-dicarbonyl compounds or derivatives thereof in a [3+3] atom fragment synthesis, which is the main strategy for the preparation of pyrimidine compounds. β-Alkoxyvinyl ketones, however, allow the possibility of comparative studies of cyclization versus *N*-alkylation, because it has been demonstrated that these enones react quickly with weak nucleophiles such as ureas.[17] An alternative for this reaction is the Biginelli synthesis, which is a condensation reaction of a 1,3-dicarbonyl compound with an aldehyde and a urea or thiourea.[18] An example of this reaction was carried out by Uray et al.:[18] An acetylcarboxylic ester was condensed with an aldehyde and methylurea to give a series of N^1-methyl-dihydropyrimidin-2-ones. This reaction is limited, because it requires an aromatic aldehyde, and the final product bears a carboxylic ester at C-5 of the dihydropyrimidine ring.[18] Thus, most *N*-alkylated pyrimidin-2-ones are obtained from S_N2 displacement of an electrophile, such as a diazoalkane,[14] alkyl halide,[15] alkyl sulfate, and alkyl phosphate,[16] with the pyrimidine reacting as the nucleophile. The chemoselectivity of *N*-alkylations has been the focus of many studies, and these have shown that, in general, by using the HSAB method[19] the *N*-alkylation of pyrimidin-2-ones gives N^1-alkylation, whereas the *N*-alkylation of pyrimidin-4-ones furnishes N^3-alkylation.[19] To the best of our knowledge, a comparative

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study involving the *N*-alkylation of pyrimidin-2-ones and the cyclocondensation of a 1,3-dielectrophile, such as an enone, β-dicarbonyl compound, or derivatives thereof with nonsymmetric ureas has not yet been carried out.

In this context, this study aims to compare the chemoselectivity and yields of the synthesis of a series of *N*-methyl-(allyl)-4-(trihalomethyl)-1*H*-pyrimidin-2-ones carried out by the cyclocondensation of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones with *N*-methyl(allyl)urea and by the *N*-alkylation of 4-(trihalomethyl)-1*H*-pyrimidin-2-ones with methyl iodide and allyl bromide.

Results and Discussion

Scheme 1 outlines the synthesis of pyrimidinones **3a**–**c** and **4a**–**c** and the corresponding *N*-alkyl derivatives. The pyrimidinones **3a**–**c** and **4a**–**c**, used as precursors for the *N*-alkylation reactions, were obtained by the condensation reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones **1a**–**c** and **2a**–**c**[20] with urea using the procedure reported in a previous paper (Scheme 1).[21]

The pyrimidinones **5**–**8**, **13c**, and **15c** were synthesized by condensation reactions of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones **1a**–**c** and **2a**–**c**[20] with excess *N*-methyl- and *N*-allylureas in methanol in the presence of hydrochloric acid.

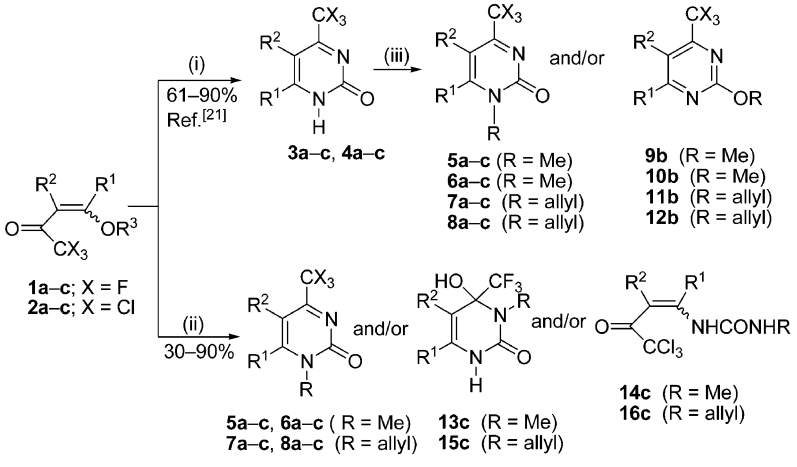
Table 1 shows the optimized reaction conditions for the cyclocondensation reactions of enones **1a**–**c** and **2a**–**c** with *N*-methyl- (Entries 1–7 and 15) and *N*-allylureas (Entries 8–14 and 16). It can be observed that the amount of solvent and acid greatly influences the reaction yields and the proportion of isomers obtained. In addition, the substituents at the α- and β-positions of the enones also influence the reaction yields and the proportion of *N*-alkylated products. Thus, the reaction conditions had to be optimized for each substrate. The reactions were carried out at reflux for 20 h with a dinucleophile/trihalomethylated enone molar ratio of 2:1. Different amounts of solvent (methanol) and concentrated hydrochloric acid were tested for each substrate in order to optimize the yields, as shown in Table 1.

Table 1. Optimized reaction conditions for the condensation reaction of enones **1a**–**c** and **2a**–**c** with *N*-methyl- and *N*-allylurea.[a]

Entry	Compound	Urea	HCl [mL]	MeOH [mL]	Product	Yield [%]
1	**1a**	*N*-Me	2.0	10	**5a**	65
2	**1b**	*N*-Me	1.0	10	**5b**	85
3	**1c**	*N*-Me	15.0	20	**5c**	75
4	**2a**	*N*-Me	2.0	10	**6a**	70
5	**2b**	*N*-Me	2.0	10	**6b**	45
6	**2c**	*N*-Me	10.0	15	**6c**	60
7	**1c**	*N*-Me	1.0	10	**13c**	80
8	**1a**	*N*-allyl	2.0	10	**7a**	90
9	**1b**	*N*-allyl	5.0	20	**7b**	90
10	**1c**	*N*-allyl	15.0	10	**7c**	70
11	**2a**	*N*-allyl	2.0	10	**8a**	70
12	**2b**	*N*-allyl	2.0	20	**8b**	30
13	**2c**	*N*-allyl	10.0	15	**8c**	60
14	**1c**	*N*-allyl	2.5	10	**15c**	75
15	**2c**	*N*-Me	1.0	10	**14c**	30
16	**2c**	*N*-allyl	1.0	10	**16c**	30

[a] Reactions were carried out at reflux for 20 h with 2.5 mmol of compound **1** or **2** and 5.0 mmol of the urea.

Table 2 shows the results from reactions performed to optimize the production of **7b** from the reaction of the enone **1b** with *N*-allylurea. Products **6b** and **8b** were obtained in low yields (30–45%) due to the formation of 1,1,1-trichloropentane-2,4-dione as a side-product, obtained from the hydrolysis of enone **2b**.



Compound	R^1	R^2	R^3
a	H	H	Et
b	Me	H	Me
c	H	Me	Et

X	Compounds
F	**1**, **3**, **5**, **7**, **9**, **11**
Cl	**2**, **4**, **6**, **8**, **10**, **12**

Scheme 1. General scheme for the synthesis of all compounds. Reaction conditions: (i) urea, MeOH, HCl, reflux, 20h; (ii) methyl- or allylurea, MeOH, HCl, reflux, 20 h; (iii) methyl iodide or allyl bromide, K_2CO_3, acetone, reflux, 20 h.

Table 2. Optimization reactions for the synthesis of compound **7b**.[a]

Entry	Compound	Urea	HCl [mL]	MeOH [mL]	Yield of **7b** [%]
1	**1b**	*N*-allyl	1.0	20	50
2	**1b**	*N*-allyl	3.0	20	60
3	**1b**	*N*-allyl	4.0	20	65
4	**1b**	*N*-allyl	5.0	20	90
5	**1b**	*N*-allyl	10.0	20	83

[a] Reactions carried out at reflux for 20 h with 5 mmol of compound **1b** and 10 mmol of *N*-allylurea.

For the cyclocondensation reaction of enones **1c** and **2c**, the amount of acid and solvent greatly influenced the reaction products. For example, the reactions of **1c** with a low concentration of hydrochloric acid and *N*-methyl- and *N*-allylureas favored the formation of dihydropyrimidinones **13c** and **15c**, respectively. Under the conditions of Entry 1 (Table 3), compound **13c** was the only isolated product. When a higher concentration of hydrochloric acid was used, only **5c** and **7c** were obtained (Entry 6). However, with an intermediate concentration, mixtures of products **5c/13c** and **7c/15c** were obtained. Table 3 shows the results from the optimization reactions used to obtain products **5c** and **13c**.

Table 3. Optimization reactions for the synthesis of products **5c** and **13c**.[a]

Entry	Compound	Urea	HCl [mL]	MeOH [mL]	Isomer composition [%]	
					5c	**13c**
1	**1c**	*N*-Me	1.0	20	0	100[b]
2	**1c**	*N*-Me	2.5	20	20	80
3	**1c**	*N*-Me	2.5	10	50	50
4	**1c**	*N*-Me	5.0	20	70	30
5	**1c**	*N*-Me	10.0	20	90	10
6	**1c**	*N*-Me	15.0	20	100[c]	0

[a] Reactions carried out at reflux for 20 h with 2.5 mmol of compound **1c** and 5 mmol of *N*-methylurea. [b] Overall yield 80%. [c] Overall yield 75%.

For the reaction of the precursor **2c** with *N*-methyl- and *N*-allylureas, when a high concentration of acid was used, compounds **6c** and **8c** were isolated, respectively, and when a low concentration of acid was used, the acyclic compounds **14c** and **16c** were obtained. The same reaction carried out with moderate concentrations of acid furnished a mixture of products **6c/14c** and **8c/16c**. A mechanism that explains the formation of the products obtained in this study is proposed in Scheme 2.

To compare the results of the cyclocondensation reactions of enones **1** and **2** with *N*-methyl- and *N*-allylureas, *N*-alkylation reactions were performed with pyrimidin-2-ones **3a**–**c** and **4a**–**c**.[21] Treatment of the pyrimidin-2-ones **3a**–**c** and **4a**–**c** with excess alkylating agent (1.5 equiv.) and potassium carbonate in acetone at reflux for 20 h provided the corresponding alkylated products. As expected for pyrimidin-2-ones under these reaction conditions, *N*-alkylation of the pyrimidinones **3a**,**c** and **4a**,**c** furnished the N^1-methylpyrimidinones **5a**,**c** and **6a**,**c** and the N^1-allylpyrimidinones **7a**,**c** and **8a**,**c** as the only isomers isolated.[22] Under the same conditions, pyrimidinones **3b** and **4b** furnished a mixture of N^1- and *O*-alkylated products **5b/9b** and **6b/10b**, as shown in Table 4. Probably, the mixture of N^1- and *O*-alkylated isomers was due to the steric effect of the methyl group at the 6-position of the pyrimidinone ring with the alkyl halides.[23] Note that for the 4-(trifluoromethyl)pyrimidinones **5b/9b** and **7b/11b**, the isomers were obtained in almost the same amounts, whereas for the 4-(trichloromethyl)-pyrimidinones **6b/10b** and **8b/12b**, the N^1-alkylated isomer was obtained in much higher yield than the *O*-alkylated isomer. The N^3-alkylated product was not observed, probably due to both steric and electron-withdrawing effects of the trihalomethyl group, which decrease the nucleophilicity of N^3. Table 4 shows the products and yields of the cyclocondensation of enones **1a**–**c** and **2a**–**c** with *N*-methyl- and *N*-allylureas and the *N*-alkylation of pyrimidinones **3a**–**c** and **4a**–**c** with methyl iodide and allyl bromide.

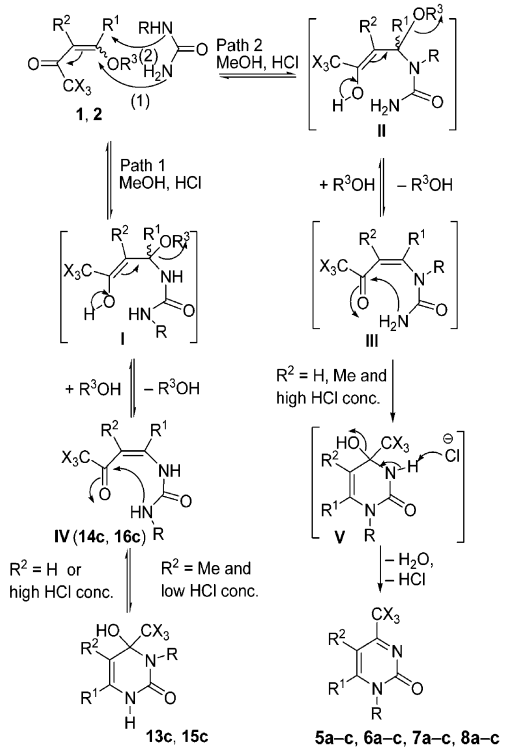
Table 4. Products and yields for the cyclocondensation and *N*-alkylation reactions.

Entry	Precursor	Urea	Cyclocondensation		Precursor	R–X	*N*-Alkylation	
			Yield [%]	Product[a]			Yield [%][j]	Product[k]
1	**1a**	*N*-Me	65	**5a**	**3a**	MeI	80	**5a**
2	**1b**	*N*-Me	85	**5b**	**3b**	MeI	50	**5b** + **9b** (1.3:1)
3	**1c**	*N*-Me	75	**5c**[b]	**3c**	MeI	77	**5c**
4	**1c**	*N*-Me	80	**13c**[c]	–	–	–	–
5	**2a**	*N*-Me	70	**6a**	**4a**	MeI	80	**6a**
6	**2b**	*N*-Me	45	**6b**	**4b**	MeI	60	**6b** + **10b** (4.5:1)
7	**2c**	*N*-Me	60	**6c**[d]	**4c**	MeI	60	**6c**
8	**2c**	*N*-Me	30	**14c**[e]	–	–	–	–
9	**1a**	*N*-allyl	90	**7a**	**3a**	allylBr	90	**7a**
10	**1b**	*N*-allyl	90	**7b**	**3b**	allylBr	55	**7b** + **11b** (1:1)
11	**1c**	*N*-allyl	70	**7c**[f]	**3c**	allylBr	95	**7c**
2	**1c**	*N*-allyl	75	**15c**[g]	–	–	–	–
13	**2a**	*N*-allyl	70	**8a**	**4a**	allylBr	70	**8a**
14	**2b**	*N*-allyl	30	**8b**	**4b**	allylBr	65	**8b** + **12b** (3:1)
15	**2c**	*N*-allyl	60	**8c**[h]	**4c**	allylBr	60	**8c**
16	**2c**	*N*-allyl	30	**16c**[i]	–	–	–	–

[a] Reaction conditions: [b] See Table 3, Entry 6. [c] See Table 3, Entry 1. [d] See Table 1, Entry 6. [e] See Table 1, Entry 15. [f] See Table 1, Entry 10. [g] See Table 1, Entry 14. [h] See Table 1, Entry 13. [i] See Table 1, Entry 16. [j] Yield of the *N*-alkylation step. [k] Product composition obtained by ^{1}H NMR integrals.

Reaction Mechanism

Presumably, the reaction starts with the Michael addition of the amino groups of the *N*-alkylurea at the β-carbon atom of the enone **1** or **2** furnishing both structures **I** and **II**, as shown in Scheme 2. The ether function is unstable in the presence of hydrochloric acid, and the alkoxy group is eliminated as an alcohol to give enaminones **III** and **IV**, as proven by the isolation of compounds **14c** and **16c**. The enaminone **III** was not isolated, probably because the attack of the less hindered amino group under a high concentration of HCl is faster than the cyclization of the enaminone **IV** leading to compounds **5**–**8**. When enaminone **I** bears a methyl substituent at the α-carbonyl carbon atom (R^2 = Me) and the reaction is carried out with a low concentration of acid, the N^3-alkyl-dihydropyrimidin-2-ones **13c** and **15c** are isolated as pure compounds in good yields. Compounds **13c** and **15c** were obtained, because the methyl group at the 5-position of the pyrimidine ring stabilizes the dihydropyrimidine form, probably due to the steric effect of the 5-methyl group on the trifluoromethyl and hydroxy groups. In addition, the elimination of a water molecule is not likely to occur when the reaction is carried out at low acid concentrations. Enaminones **14c** and **16c** did not further cyclize, probably because of the steric effect between the bulky trichloromethyl group and the *N*-methyl group. However, when R^2 = H or the reaction is carried out at a high acid concentration, N^3-alkylpyrimidinones **13c** and **15c** are unstable, and they may equilibrate back to the starting reagents **1** and **2** and then, according to path 2, to enaminone **III**, which cyclizes to furnish the pyrimidinones **5**–**8**.



Scheme 2. Reaction mechanism.

NMR Study

The correct position of the *N*-/*O*-methyl and *N*-/*O*-allyl groups of the *N*-/*O*-methyl(allyl)pyrimidines was determined by two-dimensional HMBC NMR experiments, as shown in Figure 1.[24] In this experiment, when the *N*-methyl or *N*-allyl groups are in the N^1 position, two cross-peaks between the hydrogen atoms of the *N*-methyl or *N*-CH_2 groups of the allyl groups and C-2 and -6 were observed. When the *N*-methyl or *N*-allyl groups are in the N^3 position, two cross-peaks between the hydrogen atoms of the *N*-methyl or *N*-CH_2 group of the allyl group and C-2 and -4 were observed. When the *O*-alkylated pyrimidine was obtained, only cross-peaks between the hydrogen atoms of the *O*-methyl or *O*-CH_2 group of the allyl group with C-2 were observed. Figure 1 shows these assignments for compounds **5b**, **9b**, and **13c**, with arrows indicating the expected cross-peaks between the hydrogen and carbon atoms mentioned above.

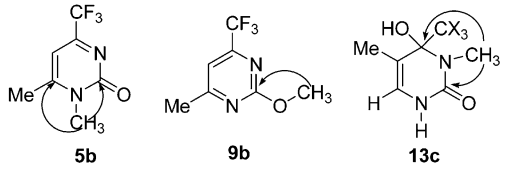


Figure 1. Strategy used for the assignment of the position of the *N*-methyl or *N*-allyl group on the pyrimidine ring by HMBC.

Note that there are significant differences in the ^{13}C NMR chemical shifts of the N^1- and *O*-alkylated isomers, as shown in Tables 5 and 6. With the exception of C-4, all the other carbon atoms of the *O*-alkylated isomer are deshielded in relation to the N^1-alkylated isomer. In particular, the chemical shifts of the *O*-methyl group of compounds **9b** and **10b** are by 21.9 and 22.3 ppm more deshielded than those of the N^1-methyl of isomers **5b** and **6b**,

Table 5. Chemical shift differences for the N^1- and *O*-alkylated isomers.

Nucleus	$\Delta\delta_{^{13}C(^1H)}$ (**9b**–**5b**) [ppm]	$\Delta\delta_{^{13}C(^1H)}$ (**10b**–**6b**) [ppm]
C-2	9.1	9.0
C-4	–4.4	–2.3
C-5 (5-H)	7.7 (027)	8.3 (0.55)
C-6	10.3	12.0
6-Me (^{1}H)	6.6 (0.05)	3.0 (–0.01)
N-Me/*O*-Me (^{1}H)	21.9 (0.33)	22.3 (0.37)

Table 6. Chemical shift differences for N^1- and *O*-alkylated isomers.

Nucleus	$\Delta\delta_{^{13}C(^1H)}$ (**11b**–**7b**) [ppm]	$\Delta\delta_{^{13}C(^1H)}$ (**12b**–**8b**) [ppm]
C-2	9.4	8.6
C-4	–3.9	–3.0
C-5 (5-H)	9.8	7.9
C-6	10.0	11.6
CF_3	1.1	0.0
6-Me (^{1}H)	4.2 (0.00)	3.6 (0.03)
N-CH_2/*O*-CH_2 (^{1}H)	20.7 (0.17)	20.1 (0.22)
=CH_2 (^{1}H)	0.8 (0.12)	0.1 (0.04)
=CH (^{1}H)	2.4 (0.18)	1.8 (0.16)

respectively. The chemical shift differences for N^1-CH_2 and O-CH_2 of the allyl group of compounds **7b/11b** and **8b/12b** follow the same trend as that observed for compounds **5b/9b** and **6b/10b**. Therefore, this study has also established the basis for an easy assignment of the position of the *N*-alkyl/*O*-alkyl group in pyrimidin-2-one.

Conclusions

We have observed that the *N*-alkylation of pyrimidines **3b** and **4b** furnished a mixture of N^1- and *O*-alkylated products, whereas the *N*-alkylation of pyrimidines **3a**,**c** and **4a**,**c** furnished only N^1-alkylated products. The cyclocondensation of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones with methyl- and allylureas, in turn, gave only N^1-alkylated products for enones **1a**,**b** and **2a**,**b**, whereas enones **1c** and **2c** (with the methyl group α to the carbonyl group) furnished N^3-alkylated pyrimidines when a low acid concentration was used and N^1-alkylated products when a high concentration of hydrochloric acid was used. As for the yields, both the *N*-alkylation of pyrimidine and the cyclocondensation of enones furnished, in most cases, good yields. However, if one considers that the *N*-alkylation products were obtained from two-step reactions (preparation of the pyrimidine and *N*-alkylation), the products from the cyclocondensation were obtained in a single reaction step, thus providing a better overall yield. In addition, significant shielding of more than 20 ppm of the ^{13}C chemical shift of the N^1-alkylated substituent was observed relative to that of the *O*-alkylated substituent of the pyrimidinones. Thus, the information from a simple hydrogen broad-band decoupled ^{13}C NMR spectrum can be used for an easy assignment of the position of the *N*-alkyl substituent in a pyrimidin-2-one.

Experimental Section

General: The syntheses of enones **1a**–**c** and **2a**–**c**[20] and pyrimidinones **3a**–**c** and **4a**–**c**[21] have been reported previously. All melting points were determined with a Reichert Thermovar apparatus and are uncorrected. Elemental analysis was performed with a Vario EL Elementar Analysensysteme. Mass spectra were registered with an HP 5973 MSD spectrometer connected to an HP 6890 GC and interfaced by a pentium PC. The GC was equipped with a split/splitless injector, an autosampler, a cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. ^1H and ^{13}C NMR and 2D HMBC spectra were acquired with a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) in [D_6]DMSO or $CDCl_3$ by using TMS as the internal reference.

General Procedure for the Preparation of Compounds 5a–c, 6a–c, 7a–c, 8a–c, and 13–16c: A mixture of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones **1a**–**c** and **2a**–**c** (5 mmol), methyl- or allylurea (10 mmol), hydrochloric acid in methanol (for the volume used, see Table 1) was heated at reflux for 20 h. The solvent was partially evaporated under reduced pressure, and cold water was added. Compounds **5a**,**c**, **6a**,**c**, **7a**, **8a**,**c**, and **13**–**16c** precipitated from solution and were collected by filtration and purified by recrystallization. Compounds **5b**, **6b**, **7b**, **7c**, and **8c** were isolated by extraction with ethyl acetate and purified by column chromatography in silica gel 60 Å (230–400 mesh) eluted with dichloromethane/methanol (95:5%, v/v).

1-Methyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (5a): This compound was obtained as a white solid in 65% yield; m.p. 170–171 °C. ^1H NMR (200 MHz, [D_6]DMSO): δ = 3.51 (s, 3 H, 1-CH_3), 6.82 (d, $^3J_{5\text{-H},6\text{-H}}$ = 6.6 Hz, 1 H, 5-H), 8.63 (d, $^3J_{6\text{-H},5\text{-H}}$ = 6.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 38.9 (1-CH_3), 98.6 (C-5), 119.5 ($^1J_{C,F}$ = 277.4 Hz, CF_3), 154.9 (C-2), 155.3 (C-6), 160.8 ($^2J_{C,F}$ = 35.0 Hz, C-4) ppm. MS (EI): *m*/*z* (%) = 178 (100) $[M]^+$, 159 (33), 150 (51). $C_6H_5F_3N_2O$ (178.11): calcd. C 40.46, H 2.83, N 15.73; found C 40.30, H 2.82, N 15.83.

1,6-Dimethyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (5b): This compound was obtained as a brown oil in 85% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, 6-CH_3), 3.62 (s, 3 H, 1-CH_3), 6.80 (s, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3 (6-CH_3), 33.1 (1-CH_3), 100.3 (C-5), 119.4 ($^1J_{C,F}$ = 277.5 Hz, CF_3), 156.3 (C-2), 161.0 ($^2J_{C,F}$ = 35.31 Hz, C-4), 162.6 (C-6) ppm. MS (EI): *m*/*z* (%) = 192 (58) $[M]^+$, 177 (100). HRMS (ESI): calcd. for $C_7H_7F_3N_2O$ $[M + H]^+$ 193.0588; found 193.0585.

1,5-Dimethyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (5c): This compound was obtained as a white solid in 75% yield; m.p. 112–115 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, 5-CH_3), 3.65 (s, 3 H, 1-CH_3), 7.95 (s, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1 (5-CH_3), 38.9 (1-CH_3), 109.7 (C-5), 119.7 ($^1J_{C,F}$ = 278.3 Hz, CF_3), 151.7 (C-6), 155.04 (C-2), 161.0 ($^2J_{C,F}$ = 34.3 Hz, C-4) ppm. MS (EI): *m*/*z* (%) = 192 (82) $[M]^+$, 123 (15), 95 (100). $C_7H_7F_3N_2O$ (192.14): calcd. C 43.76, H 3.,67, N 14.58; found C 43.63, H 3.71, N 14.54.

1-Methyl-4-(trichloromethyl)-1*H*-pyrimidin-2-one (6a): This compound was obtained as a white solid in 70% yield; m.p. 190–192 °C. ^1H NMR (200 MHz, [D_6]DMSO): δ = 3.50 (s, 3 H, 1-CH_3), 6.97 (d, $^3J_{5\text{-H},6\text{-H}}$ = 6.8 Hz, 1 H, 5-H), 8.48 (d, $^3J_{6\text{-H},5\text{-H}}$ = 6.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5 (1-CH_3), 95.5 (CCl_3), 98.1 (C-5), 153.9 (C-6), 154.5 (C-2), 170.1 (C-4) ppm. MS (EI): *m*/*z* (%) = 226 (35) $[M]^+$, 191 (100), 156 (45). $C_6H_5Cl_3N_2O$ (227.47): calcd. C 31.68, H 2.22, N 12.31; found C 31.72, H 2.27, N 12.07.

1,6-Dimethyl-4-(trichloromethyl)-1*H*-pyrimidin-2-one (6b): This compound was obtained as an oil in 45% yield. ^1H NMR (200 MHz, [D_6]DMSO): δ = 2.53 (s, 3 H, 6-CH_3), 3.63 (s, 3 H, 1-CH_3), 6.80 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (6-CH_3), 33.0 (1-CH_3), 95.2 (CCl_3), 100.3 (C-5), 156.2 (C-2), 160.8 (C-6), 169.9 (C-4) ppm. MS (EI): *m*/*z* (%) = 240 (30) $[M]^+$, 242 (24) $[M + 2]^+$, 205 (100), 156 (4), 135 (22), 123 (18). HRMS (ESI): calcd. for $C_7H_7Cl_3N_2O$ $[M + H]^+$ 240.9701; found 240.9704.

1,5-Dimethyl-4-(trichloromethyl)-1*H*-pyrimidin-2-one (6c): This compound was obtained as a white solid in 60% yield; m.p. 150–152 °C. ^1H NMR (200 MHz, [D_6]DMSO): δ = 2.45 (s, 3 H, 5-CH_3), 3.64 (s, 3 H, 1-CH_3), 7.76 (s, 1 H, H6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (5-CH_3), 38.6 (1-CH_3), 96.0 (CCl_3), 109.2 (C-5), 151.5 (C-6), 154.6 (C-2), 167.4 (C-4) ppm. MS (EI): *m*/*z* (%) = 240 (34) $[M]^+$ 205 (100), 169 (54). $C_7H_7Cl_3N_2O$ (241.50): calcd. C 34.81, H 2.92, N 11,60; found C 34.93, H 2.99, N 11.51.

1-Allyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (7a): This compound was obtained as a white solid in 90% yield; m.p. 88–90 °C. ^1H NMR (200 MHz, [D_6]DMSO): δ = 4.67 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, 1-CH_2), 5.33–5.42 (m, 2 H, =CH_2), 5.91–6.11 (m, 1 H, =CH), 6.71 (d, $^3J_{5\text{-H},6\text{-H}}$ = 6.7 Hz, 1 H, 5-H), 8.27 (d, $^3J_{6\text{-H},5\text{-H}}$ = 6.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.3 (1-CH_2), 99.5 (C-5), 119.1 ($^1J_{C,F}$ = 277.6 Hz, CF_3), 120.8 (=CH_2), 130.2 (=CH), 151.6 (C-6), 154.9 (C-2), 162.8 ($^2J_{C,F}$ = 36.4 Hz, C-4) ppm.

MS (EI): *m*/*z* (%) = 204 (53) $[M]^+$ 203 (100), 109 (23). $C_8H_7F_3N_2O$ (204.15): calcd. C 47.07, H 3.46, N 13,72; found C 46.70, H 3.43, N 13.51.

1-Allyl-6-methyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (7b): This compound was obtained as a yellow oil in 90% yield. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.49 (s, 3 H, 6-CH$_3$), 4.67 (d, J = 5.0 Hz, 2 H, 1-CH$_2$), 5.01–5.21 (m, 2 H, =CH$_2$), 5.74–5.88 (m, 1 H, =CH), 6.45 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 20.0 (6-CH$_3$), 47.8 (1-CH$_2$), 100.2 (C-5), 117.6 (=CH$_2$), 119.0 ($^1J_{C,F}$ = 274.8 Hz, CF$_3$), 129.4 (=CH), 155.4 (C-2), 160.6 ($^2J_{C,F}$ = 35.9 Hz, C-4), 163.1 (C-6) ppm. MS (EI): *m*/*z* (%) = 218 (63) $[M]^+$, 203 (100), 149 (20). HRMS (ESI): calcd. for $C_9H_9F_3N_2O$ [M + H]$^+$ 219.0744; found 219.0743.

1-Allyl-5-methyl-4-(trifluoromethyl)-1*H*-pyrimidin-2-one (7c): This compound was obtained as a white solid in 70% yield; m.p. 88–90 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.23 (s, 3 H, 5-CH$_3$), 4.64 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, 1-CH$_2$), 5.33–5.38 (m, 2 H, =CH$_2$), 5.95–6.04 (m, 1 H, =CH), 8.01 (s, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.9 (5-CH$_3$), 52.7 (1-CH$_2$), 109.8 (C-5), 119.5 ($^1J_{C,F}$ = 278.6 Hz, CF$_3$), 120.0 (=CH$_2$), 130.2 (=CH), 150.9 (C-6), 154.3 (C-2), 160.7 ($^2J_{C,F}$ = 34.4 Hz, C-4) ppm. MS (EI): *m*/*z* (%) = 218 (82) $[M]^+$, 217 (100). $C_9H_9F_3N_2O$ (218.17): calcd. C 49.55, H 4.16, N 12.84; found C 49.20, H 4.28, N 12.36.

1-Allyl-4-(trichloromethyl)-1*H*-pyrimidin-2-one (8a): This compound was obtained as a white solid in 70% yield; m.p. 135–136 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 4.65 (d, ^3J = 6.8 Hz, 2 H, 1-CH$_2$), 5.32–5.43 (m, 2 H, =CH$_2$), 5.91–6.10 (m, 1 H, =CH), 6.98 (d, $^3J_{5\text{-H},6\text{-H}}$ = 6.8 Hz, 1 H, 5-H), 8.07 (d, $^3J_{6\text{-H},5\text{-H}}$ = 6.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 52.9 (1-CH$_2$), 94.9 (CCl$_3$), 99.7 (C-5), 120.8 (=CH$_2$), 130.4 (=CH), 149.8 (C-6), 154.6 (C-2), 171.4 (C-4) ppm. $C_8H_7Cl_3N_2O$ (253.51): calcd. C 37.90, H 2.78, N 11.05; found C 37.88, H 2.94, N 11.07.

1-Allyl-6-methyl-4-(trichloromethyl)-1*H*-pyrimidin-2-one (8b): This compound was obtained as a brown oil in 30% yield. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.56 (s, 3 H, 6-CH$_3$), 4.75 (d, J = 5.2 Hz, 2 H, 1-CH$_2$), 5.17–5.32 (m, 2 H, =CH$_2$), 5.91–6.01 (m, 1 H, =CH), 6.81 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 20.6 (6-CH$_3$), 48.1 (1-CH$_2$), 95.1 (CCl$_3$), 100.4 (C-5), 118.2 (=CH$_2$), 130.0 (=CH), 155.5 (C-2), 161.1 (C-6), 170.0 (C-4) ppm. MS (EI): *m*/*z* (%) = 266 (43) $[M]^+$, 231 (100), 195 (40). HRMS (ESI): calcd. for $C_9H_9Cl_3N_2O$ [M + H]$^+$ 266.9858; found 266.9854.

1-Allyl-5-methyl-4-(trichloromethyl)-1*H*-pyrimidin-2-one (8c): This compound was obtained as a white solid in 60% yield; m.p. 96–100 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.45 (s, 3 H, 5-CH$_3$), 4.59 (d, J = 5.2 Hz, 2 H, 1-CH$_2$), 5.31–5.42 (m, 2 H, =CH$_2$), 5.89–6.06 (m, 1 H, =CH), 7.65 (s, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 16.7 (5-CH$_3$), 52.4 (1-CH$_2$), 96.0 (CCl$_3$), 109.4 (C-5), 120.7 (=CH$_2$), 130.7 (=CH), 149.8 (C-6), 154.0 (C-2), 167.3 (C-4) ppm. HRMS (ESI): calcd. for $C_9H_9Cl_3N_2O$ [M + H]$^+$ 266.9858; found 266.9858.

4-Hydroxy-3,5-dimethyl-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (13c): This compound was obtained as a white solid in 80% yield; m.p. 198–200 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.70 (d, $^4J_{H,H}$ = 1.0 Hz, 3 H, 5-CH$_3$), 2.86 (q, $J_{H,F}$ = 1.9 Hz, 3 H, 3-CH$_3$), 6.22 (dq, $^3J_{H,H}$ = 5.3, $^5J_{H,H}$ = 1.4 Hz, 1 H, CH), 7.51 (s, 1 H, OH), 8.82 (d, $^3J_{H,H}$ = 4.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 140.0 (5-CH$_3$), 27.4 (3-CH$_3$), 84.6 ($^2J_{C,F}$ = 31.4 Hz, C-4), 102.5 (C-5), 124.7 ($^1J_{C,F}$ = 294.5 Hz, CF$_3$), 125.0 (C-6), 152.1 (C-2) ppm. $C_7H_9F_3N_2O_2$ (210.15): calcd. C 40.01, H 4.32, N 13.33; found C 40.16, H 4.34, N 13.51.

1-Methyl-3-(4,4,4-trichloro-2-methyl-3-oxobuten-1-yl)urea (14c): This compound was obtained as a white solid in 30%; m.p. 184–187 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.82 (s, 3 H, 5-CH$_3$), 2.72 (d, $^3J_{H,NH}$ = 8.9 Hz, 3 H, NHC*H*$_3$), 6.73 (q, $^3J_{NH,CH_3}$ = 4.4 Hz, 1 H, N*H*CH$_3$), 8.59 (d, $^3J_{H,NH}$ = 12.0 Hz, 1 H, 6-H), 9.31 (d, $^3J_{NH,H}$ = 12.2 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 11.5 (5-CH$_3$), 26.5 (NHC*H*$_3$), 96.4 (CCl$_3$), 100.4 (C-5), 143.4 (C-6), 153.4 (C-2), 180.5 (C-4) ppm. MS (EI): *m*/*z* (%) = 258 (2) $[M]^+$, 141 (43), 84 (100). HRMS (ESI): calcd. for $C_7H_9Cl_3N_2O_2$ [M + H]$^+$ 258.9808; found 258.9804.

3-Allyl-4-hydroxy-5-methyl-4-(trifluoromethyl)-3,4-dihydro-1*H*-pyrimidin-2-one (15c): This compound was obtained as a white solid in 75% yield; m.p. 112–115 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.79 (d, $^5J_{H,OH}$ = 0.8 Hz, 3 H, 5-CH$_3$), 3.98–4.29 (m, 2 H, 3-CH$_2$), 4.93–5.12 (m, 2 H, =CH$_2$), 5.77–5.91 (m, 1 H, =CH), 6.34 (dq, $^3J_{H,H}$ = 6.0 Hz, $^5J_{H,H}$ = 1.4 Hz, 1 H, 6-H), 6.62 (d, $^5J_{OH,H}$ = 0.8 Hz, 1 H, OH), 8.21 (s, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.4 (5-CH$_3$), 44.6 (1-CH$_2$), 86.5 ($^2J_{C,F}$ = 31.8 Hz, C-4), 103.9 (C-5), 115.8 (=CH$_2$), 125.9 ($^1J_{C,F}$ = 293.1 Hz, CF$_3$), 126.3 (C-6), 136.9 (=CH), 152.8 (C-2) ppm. MS (EI): *m*/*z* (%) = 236 (7) $[M]^+$, 167 (100). $C_9H_{11}F_3N_2O_2$ (236.19): calcd. C 45.77, H 4.69, N 11.86; found C 45.74, H 4,32, N 11.76.

1-Allyl-3-(4,4,4-trichloro-2-methyl-3-oxobuten-1-yl)urea (16c): This compound was obtained as a white solid in 30% yield; m.p. 124–128 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.82 (s, 3 H, 5-CH$_3$), 3.77 (t, $^3J_{H,H}$ = 5.3 Hz, 2 H, NHC*H*$_2$), 5.05–5.19 (m, 2 H, =CH$_2$), 5.74–5.90 (m, 1 H, =CH), 7.00 (t, $^3J_{H,H}$ = 5.5 Hz, 1 H, N*H*CH$_2$), 8.46 (d, $^3J_{H,NH}$ = 12.1 Hz, 1 H, 6-H), 9.28 (d, $^3J_{NH,H}$ = 12.1 Hz, 1 H, NH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 11.5 (5-CH$_3$), 41.8 (NHCH$_2$), 96.5 (CCl$_3$), 100.9 (C-5), 115.4 (=CH$_2$), 135.1 (=CH), 143.2 (C-6), 152.8 (C-2), 180.6 (C-4) ppm. MS (EI): *m*/*z* (%) = 284 (3) $[M]^+$, 167 (31), 84 (100). HRMS (ESI): calcd. for $C_9H_{11}Cl_3N_2O_2$ [M + H]$^+$ 284.9969; found 284.9964.

General Procedure for the *N*-Alkylation of 4-(Trihalomethyl)-1*H*-pyrimidin-2-ones 3a–c and 4a–c: A mixture of pyrimidinones **3a**–**c** and **4a**–**c** (2.5 mmol), acetone (10 mL), allyl bromide or methyl iodide (3.75 mmol), and potassium carbonate (0.3 g, 3.0 mmol) was heated at reflux for 20 h. The mixture was filtered and concentrated under reduced pressure. Water was added to the residue and the mixture extracted with ethyl acetate (2 × 15 mL). The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. Compounds **5a**,**c**, **6a**,**c**, **7a**,**c**, and **8a**,**c** were obtained as solids and purified by recrystallization from hexane/ethyl acetate. Compounds **9**–**12b** were obtained as oils and purified by column chromatography in silica gel 60 Å (230–400 mesh) using dichloromethane to elute the compounds.

2-Methoxy-6-methyl-4-(trifluoromethyl)pyrimidine (9b): This compound was obtained as a mixture of **5b** and **9b** as a brown oil in 22% yield (see Table 4, Entry 2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.48 (s, 3 H, 6-CH$_3$), 3.95 (s, 3 H, 2-CH$_3$), 7.07 (s, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 27.9 (6-CH$_3$), 55.0 (OCH$_3$), 108.0 (C-5), 120.0 ($^1J_{C,F}$ = 274.84 Hz, CF$_3$), 165.4 (C-2), 156.6 ($^2J_{C,F}$ = 36.03 Hz, C-4), 172.9 (C-6) ppm.

2-Methoxy-6-methyl-4-(trichloromethyl)pyrimidine (10b): This compound was obtained as a mixture of **6b** and **10b** as a brown oil in 11% yield (see Table 4, Entry 6). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.52 (s, 3 H, 6-CH$_3$), 4.00 (s, 3 H, 2-CH$_3$), 7.35 (s, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 24.5 (6-CH$_3$), 55.3 (OCH$_3$), 95.3 (CCl$_3$), 108.6 (C-5), 165.2 (C-2), 167.6 (C-4), 172.8 (C-6) ppm.

2-(Allyloxy)-6-methyl-4-(trifluoromethyl)pyrimidine (11b): This compound was obtained as a mixture of **7b** and **11b** as a brown oil in 27.5% yield (see Table 4, Entry 10). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.49 (s, 3 H, 6-CH$_3$), 4.84 (d, J = 4.6 Hz, 2 H, 2-

CH_2), 5.09–5.37 (m, 2 H, $=CH_2$), 5.98–5.99 (m, 1 H, =CH), 7.06 (s, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2 (6-CH_3), 68.5 (OCH_2), 110.0 (C-5), 118.4 ($=CH_2$), 120.1 ($^1J_{C,F}$ = 274.8 Hz, CF_3), 131.8 (=CH), 156.7 ($^2J_{C,F}$ = 35.8 Hz, C-4), 164.8 (C-2), 173.1 (C-6) ppm.

2-(Allyloxy)-6-methyl-4-(trichloromethyl)pyrimidine (12b): This compound was obtained as a mixture of **8b** and **12b** as an oil in 16% yield (see Table 4, Entry 14). ^1H NMR (200 MHz, [D_6]-DMSO): δ = 2.59 (s, 3 H, 6-CH_3). 4.97 (d, J = 5.7 Hz, 2 H, 2-CH_2), 5.26–5.51 (m, 2 H, $=CH_2$), 6.02–6.21 (m, 1 H, =CH), 7.43 (s, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2 (6-CH_3), 68.2 (OCH_2), 95.1 (CCl_3), 108.3 (C-5), 118.3 ($=CH_2$), 131.8 (=CH), 164.1 (C-2), 167.0 (C-4), 172.7 (C-6) ppm. MS (EI): m/z (%) = 266 (18) $[M]^+$, 251 (13), 231 (100), 210 (35), 195 (25), 149 (56).

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