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Cyclocondensation between fatty acid hydrazides and 1,1,1trifluoro-4-alkoxy-3-alken-2-ones: Introducing a trifluoromethylated head onto fatty acid moieties

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Supplemental data (full experimental details and characterization of title compounds) for this article can be access on the publisher's website. <TQ: The publisher's website will be a live link.>

ABSTRACT

This paper reports the regioselective synthesis of new trifluoromethylated lipid derivatives, namely, 1-(5-hydroxy-5-trifluoromethyl-3-alkyl-4,5-dihydro-1*H*-pyrazol-1-yl)alkan-1-ones, via cyclocondensation reactions between a series of fatty hydrazides (palmitoyl, stearoyl, and oleoyl hydrazides) obtained from fatty acids from renewable resources (1,1,1-trifluoro-4-alkoxy-3-alken-2-ones [F₃CC(O)CH=C(R¹)OR, where R¹ = H and R = Et; R¹ = -(CH₂)₆CH₃, -(CH₂)₉CH₃, -(CH₂)₉CH₃, -(CH₂)₉CH₃, -(CH₂)₉CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, -(CH₂)₁₂CH₃, -(CH₂)₂Ph]; and R = Me). Experimental observations showed that the lipophilic characteristic of 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles (**5**–**7**) prevent the acid catalyzed dehydration to aromatization of 1*H*-pyrazole ring, although in some cyclocondensations a proportion of the aromatic derivative 1-(5-trifluoromethyl-3-alkyl-1*H*-pyrazol-1-yl)alkan-1-one was obtained. All products were characterized using multinuclear (¹H, ¹³C, ¹⁹F) NMR spectroscopy.

GRAPHICAL ABSTRACT



KEYWORDS: [3 + 2] cyclocondensation, 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones, 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles, fatty hydrazides

Introduction

Cyclocondensation between CF_3 -containing dieletrophiles, such as 4,4,4-trifluoro-1aryl/heteroaryl-1,3-butanediones, 1,1,1-trifluoro-2,4-alkenones, and 1,1,1-trifluoro-4-methoxy-3alken-2-ones, and hydrazines has largely been used to synthesize trifluoromethyl-substituted 1Hpyrazole derivatives. Several research groups have reported results on mechanistic aspects of such reactions, involving the regio-selectivity and stability of intermediates such as hydrazone/enaminone and 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles.^[1-6] Singh,^[7] Elguero,^[8] and Norris^[9] conducted systematic studies of cyclocondensation between hydrazines and 4,4,4-trifluoro-1-aryl/heteroaryl-1,3-butanediones, 4,4-difluoro-1-phenyl-1,3-butanedione, 1,1,1-trifluoro-2,4-pentanedione, and 1,1,1,5,5,5-hexafluoropentanedione. Each author concluded that the orientation of the first attack of the nucleophilic nitrogen depends on the substituent in the hydrazine, but not as a kinetic parameter to reactivity, but rather mainly due to the thermodynamic stability of 3,5-dihydroxypyrazolidines in equilibrium and posterior imine bond formation. This approach was revisited by Singh and Elguero,^[10] who studied reactions between aryl and heteroarylhydrazines and 1-aryl-4,4,4-trifluoro-2,3-butanediones under neutral and acidic conditions, however, they did not mention the pH of the reaction solutions used. The authors were able to synthesize and isolate a wide range of 3- and 5-trifluoromethyl-1Hpyrazoles, and concluded that the synthetic approach is tunable on three parameters: the pH conditions, i.e., using neutral (without the addition of acid) or acidic media; and the electronwithdrawing effect of the substituent on the hydrazine moiety and on the phenyl ring of the 1,3-Volkova^[11] reported reactions between 4,4,4-trifluoro-1-(thien-2-yl)-1,3butanedione. butanedione and hydrazines, and initially demonstrated that a trifluoromethyl-substituted carbonyl can be attacked by molecules of water or alcohol solvents presented in a reaction medium, which changes the reactivity of electrophilic carbonyls; the reactions were conducted in ethyl ether, leading to 5-hydroxy-3-(thien-2-yl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole, which can then be subjected to dehydration to form the respective tautomerizable 3(5)-(thien-2yl)-5(3)-trifluoromethyl-1*H*-pyrazole. Ros and Pons^[12] reacted 2-hydroxyethylhydrazine with 4,4,4-trifluoro-1-(pyridin-2-yl)-1,3-butanedione in ethanol, and were able to tune the results by controlling the reaction temperature; however, they obtained only the 1,5-regioisomer as 5hydroxy-1-(2-hydroxyethyl)-3-(pyridin-2-yl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole when reactions were conducted at 0°C for 7h or as 2-[3-(pyridin-2-yl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]ethanol when reactions were conducted at 25°C for 15h. Scheme 1 summarizes these results.

Dinucleophilic hydrazides or hydrazide-like compounds have been systematically employed in reactions with CF₃-containing dieletrophiles to synthesize 1*H*-pyrazoles and polyheterocyclic systems with desirable biological or electronic properties.^[13–19] However, none of the cited studies described the production of regioisomers 1*H*-pyrazoles.

The reactivities of hydrazides and hydrazide-like nitrogens are well differentiated, so that the first nucleophilic attack is always from an unsubstituted nitrogen, leading to an imine bond, hydrazone (semicarbazone, thiosemicarbazone), and then a cyclization product via hemiaminal moiety formation; ultimately, this forms stable 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole derivatives, as shown in Scheme 2.

Moreover, renewable resources are increasingly being used in the production of useful chemicals. For example, vegetable oils and carbohydrates can be used as feedstocks for the manufacture of a variety of sustainable materials and products, including fine chemicals and polymeric materials.^[20] Since the 1950s, oleochemistry has grown into a major field, both at

research institutes and in industries. A large variety of products based on fats and oils have been developed, including biodiesel, surfactants, emollients, biodegradable mineral oil replacements for lubricants, polymer supplies, and fine chemicals.^[21–23]

In this context, we decided to apply the cyclocondensation [3 + 2] between 1,1,1trifluoro-4-alkoxyalk-3-en-2-ones and fatty hydrazides to obtain a series of new oleochemicals. Specifically, we used a large set of 1,1,1-trifluoro-4-alkoxyalk-3-en-2-ones (**1a-g**), mostly derived from unbranched, long-chain 2-alkenones, with ecofriendly palmitic, stearic, and oleic fatty hydrazides. Cyclocondensation between 4-etoxy-1,1,1-trifluorobut-3-en-2-one and the series of fatty hydrazides is a synthetic approach to introduce an unbranched trifluoromethylated head to a natural fatty moiety, leading to new, interesting hybrid oleochemicals.

Results and discussion

A series of 1,1,1-trifluoro-4-methoxyalk-3-en-2-ones (**1b-g**) were obtained via trifluoroacetylation of the respective dimethoxy acetal derivatives.^[24] The 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1a**) was obtained from ethyl vinyl ether trifluoroacetylation, as described previously.^[25] The fatty hydrazides were obtained by hydrazinolysis of the respective fatty methyl alkanoates, as described previously.^[26] This step was the most challenging in the proposed route. Although there were no problems with the saturated esters, the process of reduction of oleic acid derivatives competes for the hydrazine hydrate of the medium (for the reduction of the double bond), and so it is necessary to strictly control the temperature and reaction time. Higher temperatures or longer reaction periods lead to a mixture of hydrazides **3** and **4**; on the other hand, we could not obtain the pure oleyl hydrazide without it containing some amount of methyl oleate (see the spectra for compound **7**, Supplementary Material).

The reaction conditions for synthesizing 1-acyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles were adapted from a method already described in the literature, in which cyclocondensation was carried out in methanol under BF3.OEt2 catalysis.^[27] Initially, we conducted cyclocondensation between 1a and palmitoyl hydrazide (2) at a 1:1 molar ratio in 10mL ethanol, a reasonably ecofriendly solvent that solubilizes hydrazides. The reaction mixture was stirred at 25–50°C for 24h and monitored by TLC; the reaction proceeded without consuming dielectrophile 1a. Cyclocondensation occurred only at ethanol reflux for 24h even without adding a catalyst, leading to 5-hydroxy-5-trifluoromethyl-1-palmitoyl-4,5-dihydro-1Hpyrazole (5a), which precipitated out at 80% yield. Changing the reaction solvent did not improve its performance. Adding 10 wt.% BF₃.OEt₂in EtOH did not change the reaction results; in fact, the product obtained under these conditions had to be recrystallized after precipitation in summarizes the reaction conditions optimized for reaction medium. Table 1 the cyclocondensation to obtain 1-acyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles. Next, we verified whether the same conditions could be used with dielectrophilic precursors with a long-chain substituent. A 1:1 mixture of 1,1,1-trifluoro-4-methoxypentadec-3-en-2-one (1e) and palmitoyl hydrazide (2) in EtOH was stirred at 80°C for 24h, leading to 5-hydroxy-5trifluoromethyl-1-palmitoyl-3-undecyl-4,5-dihydro-1H-pyrazole (5e) at 78% yield. The reaction conditions shown in Table 1 (entry 4) were extended to cyclocondensations between series **1a-g** and fatty hydrazides to afford the respective 1-acyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles 5–7 (Scheme 3).

The structure of each product was assigned based on NMR spectroscopy and LC-MS/MS data. The ¹H NMR spectra for 1-acyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole **5–7** showed a general feature, displaying the signals as doublets with characteristic geminal coupling

constant of 19Hz related to diastereotopic hydrogens at C-4 on the 1*H*-pyrazole ring at 3.07 and 3.21ppm (**Figure 1**).

Signals due to diasterotopic hydrogens from **5a** appeared to be more deshielded at 3.19ppm, as doublets of multiplets, and at 3.35ppm, as doublets of doublets. This demonstrated that alkyl substituents at the 3-position of the 1*H*-pyrazole ring have a shielding effect on hydrogen nuclei. Further, the multiplicity of the more shielded signal indicated coupling with fluorine nuclei in the trifluoromethyl group with ${}^{4}J_{HF} \sim 1.6Hz$, approximately the same value of the ${}^{3}J_{HH}$ between H-3 and H-4. In this spectrum, it was also possible to observe the signals of diastereotopic α -hydrogens to the carbonyl of the hydrazide portion as doublets of multiplets between 2.6–2.8ppm (**Figure 1**). The 13 C NMR spectra showed the characteristic signals for each derivative series. In general, the quartet related to the CF₃ group displayed at about δ 123ppm with J_{CF} 288Hz, that related to C-5 of the 1*H*-pyrazole ring was at about δ 90ppm with ${}^{3}J_{CF}$ 34Hz, the singlet signal related to the carboxyl group was at about δ 176ppm, and a cluster of overlapping signals related to the long methylene chain was observed between 22 and 35ppm.

Some attempts were made to dehydrate/aromatize the 1-(3-heptyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-yl)hexadecan-1-one (**5b**), using a mild method that would not also cause hydrolysis of the alkanoyl moiety from the 1*H*-pyrazole ring.^[13,15] We were unable to completely convert 4,5-dihydro-1*H*-pyrazole derivatives **5–7** into their respective dehydrated/aromatized derivatives. **Figure 2** shows the ¹H NMR spectra of the mixture obtained after a conventional sulfuric acid dehydration of compound **5b** at 25°C.

Experimental

The 1,1,1-trifluoro-4-methoxy-3-alken-2-ones (**1a-g**) were synthesized according to previous procedures developed in our laboratory.^[24] ¹H,¹³C and ¹⁹F spectra were acquired at 305K on a Bruker Ascend Avance III 400 spectrometer using a 5mm dual probe. Chemical shifts (δ) are reported in ppm from tetramethylsilane (TMS), and coupling constants (*J*) are given in Hz. Compounds **5–8** were dissolved in acetonitrile (Merck, USA), 50% (v/v) with deionized water and 0.1% formic acid. The dissolved compounds were infused individually into the ESI source using a syringe pump (Harvard Apparatus) at a flow rate of 150 µL min⁻¹. ESI(+)-MS were acquired using a hybrid high-resolution and high-accuracy (5 µL/L) microTof (Q-TOF) mass spectrometer (Bruker® Scientific). Cone voltages were set to + 3500V and + 40V, respectively, with a desolvation temperature of 100°C. Diagnostic ions were identified by comparing experimental to theoretical ESI(+)-MS/MS.

General procedure for 1-acyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1Hpyrazole synthesis

A solution of 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones (**1a-g**) (3 mmol) and NH₂NH₂.HCl (3 mmol) in 10mL EtOH was stirred at 80°C until complete dissolution, and the resulting mixture was stirred for 16h. After the reaction was completed, the mixture was cooled and the 1*H*-pyrazole derivative product was precipitated out, filtered off, and washed with cooled EtOH and water. Products were analyzed without further purification. Spectroscopic data are shown in the Supplementary Information.

1-(5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)hexadecan-1-one (**5a**) was obtained (80%) as a yellowish wax (EtOH). ¹H NMR (400MHz, CDCl₃): δ 6.94 (t, ³*J*_{*HH*} 1.5Hz, 1H, H3), 3.35 (m, ²*J*_{*HH*} 19.5Hz, 1H, H4b), 3.17 (d, ²*J*_{*HH*} 19.5Hz, 1H, H4a), 2.71 (m, 2H, αCH₂),

1.68 (q, ${}^{3}J_{HH}$ 7.5Hz, 2H, βCH₂), 1.41–1.17 (m, 22H, CH₂), 0.89 (t, ${}^{3}J_{HH}$ 7.1Hz, 6H, CH₃); 13 C NMR(100MHz CDCl₃): δ 176.2 (CO), 144.4 (C3), 123.3 (q, J_{CF} 287.1Hz, CF₃), 90.0 (q, ${}^{2}J_{CF}$ 34.5Hz, C5), 44.7 (C4), 22.9–35.1 (CH₂), 14.0 (CH₃); 19 F NMR (376.5MHz CDCl₃) δ ppm: – 81.8 (s). C₂₀H₃₆F₃N₂O₂ calcd. mass 393.2729g .mol⁻¹. Found: 393.2844g .mol⁻¹.

1-(3-heptyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-yl)hexadecan-1-one (**5b**) was obtained (80%) as a yellow wax (EtOH). ¹H NMR (400MHz, CDCl₃): δ 3.21 (d, ²*J*_{HH} 18.9Hz, 1H, H4b), 3.07 (d, ²*J*_{HH} 19.1Hz, 1H, H4a), 2.64 (m, 2H, α CH₂), 2.35 (t, ³*J*_{HH} 7.75Hz, 2H, α CH₂), 1.63 (m, 4H, β CH₂), 1.40–1.21 (m, 31H, CH₂), 0.89 (m, 6H, CH₃). ¹³C NMR (100MHz, CDCl₃): δ 175.8 (CO), 157.7 (C3), 123.4 (q, *J*_{CF} 287.6Hz, CF₃); 91.2 (q, ²*J*_{CF} 34.1Hz, C5), 45.3 (C4), 22.6–34.7 (CH₂), 14.0 (CH₃); ¹⁹F NMR (376.5MHz CDCl₃) δ ppm: – 81.8 (s). C₂₇H₅₀F₃N₂O₂ calcd. mass 491.3819g .mol⁻¹. Found: 491.3952g .mol⁻¹.

between 1,1,1-trifluoro-4-alkoxy-3-alken-2-one Cvclocondensation 1 and fattv hydrazides 2-4 is an efficient method to synthesize 1-acyl-5-hydroxy-5-trifluoromethyl-4,5dihydro-1*H*-pyrazoles at good yields and purity. The results demonstrate the efficiency and 1,1,1-trifluoro-4-alkoxy-3-alken-2-one versatility of precursors introduce to a trifluoromethylated head into natural fatty acid moieties, producing a new class of lipophilic compounds with gelling and lubricant characteristics. Our data also endorse the high thermodynamic stability of the hemiketal/aminal C-5 moiety produced during [CCC + NN]cyclocondensation between hydrazides and perfluoroalkyl-substituted 1,3-dielectrophiles.

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References

- Desens, W.; Winterberg, M.; Büttner, S.; Michalik, D.; Saghyan, A. S.; Villinger, A.; Fischer, C.; Langer, P. *Tetrahedron* 2013, 69, 3459–3464.
- [2] Bazhin, D. N.; Kudiakova, Y. S.; Röschenthaler, G. V.; Burgart, Y. V.; Slepukhin, P. A.; Isenov, M. L.; Saloutin, V. I.; Charushin, V. N. Eur. J. Org. Chem. 2015, 5236–5245.
- [3] Usachev, B. I.; Obydennov, D. L.; Sosnovskikh, V. Ya. J. Fluorine Chem. 2012, 135, 278– 284.
- [4] Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A.C.; Villanova, S.; Murguía, M. J. Org. Chem. 2008, 73, 3523–3529.
- [5] Boltacheva, N. S.; Dianova, L. N.; Slepukhin, P. A.; Filyakova, V. I.; Bakulev, V. A.; Charushin, V. N. Russ. J. Org. Chem. 2014, 50, 767–777.
- [6] Pace, A.; Buscemi, S.; Vivona, N. Org. Prep. Proc. Int. 2007, 39, 1-70.
- [7] Singh, S. P.; Kumar, D.; Jones, B. G.; Threadgill, M. D. J. Fluorine Chem. 1999, 94, 199– 203.
- [8] Singh, S. P.; Kumar, D.; Batra, H.; Naithani, R.; Rozas, I.; Elguero, J. Can. J. Chem. 2000, 78,1109–1120.
- [9] Norris, T.; Colon-Cruz, R.; Ripin, D. H. P. Org. Biomol. Chem. 2005, 3, 1844–1849.
- [10] Singh, S. P.; Kumar, V.; Aggarwal, R.; Elguero, J. J. Heterocycl. Chem. 2006, 43, 1003– 1014.
- [11] Volkova, K. A.; Volkov, A. N.; Albanov, A. I.; Nakhmanovich, A. S.; Lopyrev, V. A. Russ. J. Gen. Chem. 2003, 73,1623–1626.
- [12] Montoya, V.; Pons, J.; García-Antón, J.; Solans, X.; Font_Bardia, M.; Ros, J. J. Fluorine Chem. 2007, 128, 1007–1011.
- [13] Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P.; Naue, J. A. J. Fluorine Chem. 1998, 92, 23–26.
- [14] Bonacorso, H. G.; Oliveira, M. R.; Wentz, A. P.; Wastowski, A. D.; Oliveira, A. B.; Höerner, M.; Zanatta, N.; Martins, M. A. P. J. Fluorine Chem. 1999, 55, 345–352.
- [15] Bonacorso, H. G.; Oliveira, M. R.; Costa, M. B.; Silva, L. B.; Zanatta, N.; Martins, M. A. P.; Flores, A. F. C. J. Braz. Chem. Soc. 2005, 16, 868–873.
- [16] Bonacorso, H. G.; Oliveira, M. R.; Costa, M. B.; Silva, L. B.; Wastowski, A. D.; Zanatta, N.; Martins, M.A.P. J. Heterocycl. Chem. 2005, 42, 631–637.
- [17] Pakalnis, V. V.; Zerova, I. V.; Yakimovitch, S. I.; Alekseyev, V. V. Chem. Heterocycl. Compd. 2008, 44, 606–614.
- [18] Aggarwal, R.; Kumar, R.; Kumar, S.; Garg, G.; Mahajan, R.; Sharma, J. J. Fluorine Chem. 2011, 132, 965–972.
- [19] Bonacorso, H. G.; Pittaluga, E. P.; Alves, S. H.; Schaffer, L. F.; Cavinatto, S.; Porte, L. M. F.; Paim, G. R.; Martins, M. A. P.; Zanatta, N. Arkivoc 2012, 62–75.
- [20] Oh, Y. H.; Eom, I. Y.; Joo, J. C.; Yu, J. H.; Song, B. K.; Lee, S. H.; Hong, S. H.; Park, S. J. Korean J. Chem. Eng. 2015, 32,1945–1959.
- [21] Liu, H.; Cheng, T.; Xian, M.; Cao, Y.; Fang, F.; Zu, H. Biotechnol. Adv. 2014, 32, 382–389.

- [22] McFarlane, J. Soybean Oil Derivatives for Fuel and Chemical Feedstocks. In *Soybean–Bio-Active Compounds*; El-Shemy, H. A., Ed.; InTech, 2013; pp 111–133.
- [23] Metzger, J. O. Eur. J. Lipid Sci. Technol. 2009, 111, 865–876.
- [24] Flores, A. F. C.; Brondani, S.; Zanatta, N.; Rosa, A.; Martins, M. A. P Tetrahedron Lett. 2002, 43, 8701–8705.
- [25] Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. Chem. Lett. 1976, 409-502.
- [26] Rauf, A.; Sharma, S.; Gangal, S. Arkivoc 2007, 137–147.
- [27] Beck, P.; Santos, J. M.; Kuhn, B. L.; Moreira, D. N.; Flores, A. F. C.; Martins, M. A. P.; D'oca, M. G. M.; Piovesan, L. A. J. Braz. Chem. Soc. 2012, 23, 2122–2127.

Entry	Solvent	Solvent volume	Temperature (°C)	Time (h)	Yield (%)
		(mL)			
1	EtOH	5	50	16	_a
2	EtOH	10	50	24	-a
3	EtOH	20	50	24	-a
4	EtOH	10	80	24	80
5	EtOH	10	80	24	65 ^b
6	MeOH	10	65	24	53°
7	MeCN	10	80	24	45°
8	MeCN	10	80	36	82
9	АсОН	10	50	12	-d
10	iPrOH	10	80	24	75

Table 1. Optimization of reaction conditions for cyclocondensation between **1a** and palmitoyl hydrazide.

^aRecovery of starting reagents.

^bWith 10 wt.% BF₃.EtO₂. Yield after recrystallization from MeOH.

^cConversion measured by ¹H NMR.

^dMixture of products: N'-acetyl palmitoyl hydrazide, **5a**, and reactants.

Figure 1. Parallel between ¹H NMR spectra of 1-acyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles **5a** and **5b**, with projections showing the dihedral angles between the ¹H nuclei and the other substituents of the pyrazole ring.



Figure 2. ¹³C {H} NMR spectrum of a mixture of **5b** and 1-(3-heptyl-5-trifluoromethyl-1*H*-pyrazol-1-yl)hexadecan-1-one, obtained via dehydration/aromatization of 4,5-dihydro-1*H*-pyrazole**5b**with sulfuric acid.



ce

C,

Scheme 1. Synthesis of trifluoromethyl-1*H*-pyrazoles from trifluoromethyl- β -diketones and hydrazines.

1



$$\label{eq:rescaled} \begin{split} \mathbf{R} = \mathrm{CH}_3, \mathrm{CF}_3, \mathit{aryl} \ (\mathrm{Ph}, 4+\mathrm{FC}_6\mathrm{H}_4, 4-\mathrm{BrC}_6\mathrm{H}_4, 4-\mathrm{CH}_3\mathrm{OC}_6\mathrm{H}_4, 4-\mathrm{NO}_2\mathrm{C}_6\mathrm{H}_4), \ \mathit{heteroaryl} \ (\mathrm{tien-2-yl}, \ \mathrm{pyrid-2-yl}, \ \mathrm{pyrid-3-yl}, \ \mathrm{l-methyl-1}H\ \mathrm{-benzo}[d]\mathrm{imidazo-2-yl}, \ \mathrm{benzo}[d]\mathrm{tiazol-2-yl} \end{split}$$

 $R^{1} = H, CH_{3}, CH_{2}CH_{2}OH, Ph, 4-FC_{6}H_{4}, 4-ClC_{6}H_{4}, 4-NO_{2}C_{6}H_{4}, 2, 4-(NO_{2})_{2}C_{6}H_{3}, \\ benzo[d] thiazol-2-yl, quinolin-2-yl, C_{6}F_{5}, Ch_{2}CH_{2}OH, Ph, 4-FC_{6}H_{4}, 4-ClC_{6}H_{4}, 2, 4-(NO_{2})_{2}C_{6}H_{3}, \\ benzo[d] thiazol-2-yl, quinolin-2-yl, C_{6}F_{5}, Ch_{2}CH_{2}OH, Ph, 4-FC_{6}H_{4}, 4-ClC_{6}H_{4}, 2, 4-(NO_{2})_{2}C_{6}H_{3}, \\ benzo[d] thiazol-2-yl, quinolin-2-yl, C_{6}F_{5}, Ch_{2}CH_{2}OH, Ph, 4-FC_{6}H_{4}, 4-ClC_{6}H_{4}, 2, 4-(NO_{2})_{2}C_{6}H_{3}, \\ benzo[d] thiazol-2-yl, quinolin-2-yl, C_{6}F_{5}, Ch_{2}CH_{2}OH, Ph, 4-FC_{6}H_{4}, 4-ClC_{6}H_{4}, 4-NO_{2}C_{6}H_{4}, 2, 4-(NO_{2})_{2}C_{6}H_{3}, \\ benzo[d] thiazol-2-yl, quinolin-2-yl, C_{6}F_{5}, Ch_{2}CH_{2}OH, Ph, 4-FC_{6}H_{4}, 4-NO_{2}C_{6}H_{4}, 2, 4-(NO_{2})_{2}C_{6}H_{3}, \\ benzo[d] thiazol-2-yl, quinolin-2-yl, C_{6}F_{5}, Ch_{2}CH_{4}, Q_{2}CH_{4}, Q_{2}$

Scheme 2. Synthesis of trifluoromethyl-1*H*-pyrazoles from trifluoromethyl- β -diketones, hydrazides, and hydrazide-like nitrogens.



Scheme 3. Synthesis of 1-acyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole **5–7** derivatives.

