Microwave-assisted three-component coupling-addition-S_NAr (CASNAR) sequences to annelated 4*H*-thiopyran-4-ones†

Benjamin Willy,[a] Walter Frank‡[b] and Thomas J. J. Müller*[a]

Received 26th August 2009, Accepted 28th September 2009
First published as an Advance Article on the web 23rd October 2009
DOI: 10.1039/b917627f

A whole family of annelated 4*H*-thiopyran-4-ones as the core structural unit was readily synthesized in good yields by a microwave-assisted coupling-addition-S_NAr (CASNAR) sequence starting from readily available (het)aroyl chlorides, alkynes and sodium sulfide nonahydrate in a consecutive one-pot three-component reaction. All representatives display a pronounced halochromicity of the absorption bands upon protonation. According to DFT calculations, the electronic ground state of the annelated 4*H*-thiopyran-4-ones possess a considerable zwitterionic character.

Introduction

Thiopyranone is the thio homologue of pyranone, a core constituent of many natural products. In their own right, thiochromenones, benzo-annelated thiopyranones that are related to the class of flavones, are potent drug candidates and serve as key intermediates for the synthesis of biologically active compounds. As a consequence, many thiochromenones are known to exhibit antimicrobial and antifungal,[1] antibacterial,[2] antibiotic,[3] and anticarcinogenic[4] activity. Some derivatives are used as antimalaria agents,[5] and oxidized representatives reversibly inhibit the human cytomegalovirus protease.[6]

In general, 4*H*-thiochromen-4-ones are synthesized either by condensation of β-keto esters and thiophenols with polyphosphoric acid[7] or by cyclization of β-substituted cinnamates derived from thiophenols and appropriate propiolates.[5,8] Condensation and subsequent acid-mediated cyclization of lithiated intermediates derived from acetoacetanilides,[9] C(α),*N*-benzoyl hydrazones or C(α),*N*-carboalkoxy hydrazones[10] with methyl thiosalicylates also lead to the formation of 4*H*-thiochromen-4-ones. Just recently, a synthesis *via* intramolecular thiolester carbonyl olefination using *N*-phenyl(triphenylphosphorany1idene)ethenimine as a starting material was reported.[11]

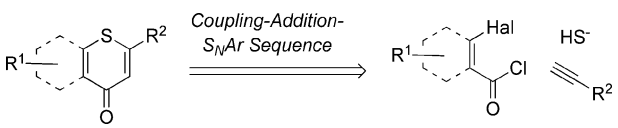
However, most of these methods could not successfully be applied to the synthesis of methoxy-substituted thioflavones.[12] Either the reported strategies require many steps or the starting materials are difficult to synthesize. Hence, due to the interesting pharmacological potential of 4*H*-thiopyran-4-one derivatives and as a part of our program to develop multi-component syntheses of heterocycles,[13] we recently communicated a novel three-component synthesis of 4*H*-thiochromen-4-ones with a highly flexible substitution pattern.[14] Here, we report the methodological extension of this innovative strategy to various classes of annelated 4*H*-thiopyran-4-ones and their optical properties.

Results and discussion

Synthesis

Alkynones are accessible by Sonogashira coupling[15] of acid chlorides with terminal alkynes.[16] However, a modified protocol with THF as the solvent using only one stoichiometrically necessary equivalent of triethylamine as the base has proven to be most favorable for successful coupling.[17] In turn, the resulting alkynones are reactive Michael acceptors ready to react with various nucleophiles[18] and dipolarophiles[19] in a one-pot fashion to give a plethora of heterocycles.

Retrosynthetically, the formation of annelated 4*H*-thiopyran-4-ones in a one-pot fashion can be perceived *via* a sequence of intramolecular nucleophilic aromatic substitutions (S_NAr) and Michael addition of hydrosulfide yielding alkynones **5** (Scheme 1). These alkynones should be accessible by Sonogashira coupling of 2-halobenzoyl chlorides **1** and terminal alkynes **2**. Prior to our studies, only a few examples of S_NAr-Michael addition of hydrosulfide to alkynones had been reported.[20] Hence, the remaining methodological challenge is the development of a general rapid one-pot three-component coupling-addition-S_NAr (CASNAR) process.



Scheme 1 Mechanistic rationale of the coupling-addition-S_NAr (CASNAR) sequence.

Therefore, *ortho*-haloaroyl chloride **1a** or **1b** was reacted with ethynyl benzene (**2a**) under modified Sonogashira conditions for 1 h at room temperature to furnish the expected alkynones **5**. Subsequently, sodium sulfide nonahydrate (**3**) and ethanol

[a]*Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstr., 1, D-40225, Düsseldorf, Germany. E-mail: ThomasJJ.Mueller@uni-duesseldorf.de; Fax: +492118114324*
[b]*Lehrstuhl für Anorganische Chemie und Strukturchemie der Heinrich-Heine-Universität Düsseldorf, Universitätsstraße, 1, D-40225, Düsseldorf, Germany*

† Electronic supplementary information (ESI) available: Experimental details, X-ray coordinates, molecular modeling coordinates and fluorescence spectrum of **4e-H**$^+$. CCDC reference numbers 754614–754615. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b917627f

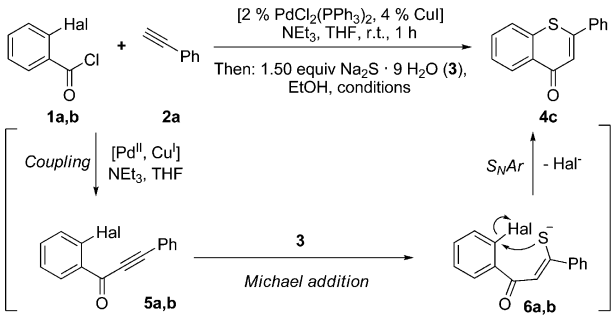
‡ X-Ray structure analyses.

Table 1 Optimization of the one-pot microwave-assisted coupling-addition-S_NAr (CASNAR) synthesis of 4*H*-thiochromen-4-one **4a** by reaction of *ortho*-halobenzoyl chlorides **1a** and **1b**, ethynyl benzene (**2a**), and $Na_2S{\cdot}9\ H_2O$ (**3**)

Entry	**1** (equiv.)	**2c** (equiv.)	**3** (equiv.)	Addition-S_NAr	**4a** Yield (%)[a]
1	**1a** (1.00)	1.00	1.10	90 °C, 120 min[b]	52
2	**1a** (1.00)	1.00	1.10	90 °C, 90 min	58
3	**1a** (1.00)	1.00	1.50	90 °C, 90 min	59
4	**1a** (1.25)	1.00	1.50	90 °C, 90 min	73
5	**1b** (1.25)	1.00	1.50	90 °C, 90 min	40

[a] Isolated yield after column chromatography on silica gel (ethyl acetate/hexanes). [b] Control experiment in an oil bath.

were added to the reaction mixture and heated in a microwave cavity to give 4*H*-thiochromen-4-one **4a** (Scheme 2, Table 1). Mechanistically, it is likely that the rapid Michael addition of the hydrosulfide ion to the alkynone **5** to give adduct **6** precedes the cyclizing S_NAr, assisted by Pd and/or Cu catalysis.

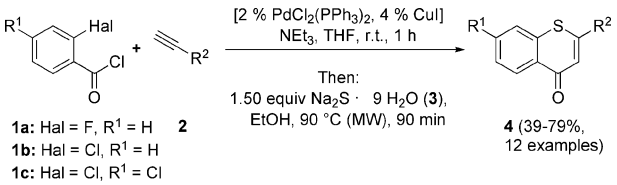


Scheme 2 Mechanistic rationale of the coupling-addition-S_NAr (CASNAR) sequence.

Dielectric heating proved to be more efficient than conductive heating in an oil bath (entries 1 and 4), but only in the concluding addition-substitution step. Sonogashira coupling proceeded smoothly at room temperature and without formation of side products. Fluorine as a leaving group was superior to chlorine (entries 4 and 5). Hence, the stage was set for a novel microwave-assisted three-component coupling-addition-S_NAr (CASNAR) synthesis of 4*H*-thiochromen-4-ones **4** in a one-pot fashion.

Therefore, the coupling of 2-halobenzoyl chlorides **1** with terminal alkynes **2** under modified Sonogashira conditions for 1 h at room temperature, and addition of sodium sulfide nonahydrate (**3**) and ethanol, with reaction for 90 min at 90 °C in a microwave cavity resulted in the formation of substituted 4*H*-thiochromen-4-ones **4** in moderate to good yields as bright yellow solids (Scheme 3, Table 2).

Interestingly, 2,4-dichlorobenzoyl chloride **1c** selectively furnished 7-chloro-substituted products (Table 2, entries 10–15) without competing S_NAr at the *para*-position. In comparison, existing protocols for the synthesis of 4*H*-thiochromen-4-one **4c** generally require several steps, sometimes harsh reaction conditions, longer reaction times and give significantly lower overall yields (Table 3). With the method described herein, the synthesis and isolation of **4c** is possible within 2 h, starting from commercially available starting materials.



Scheme 3 Coupling-addition-substitution (CASNAR) sequence to yield substituted 4*H*-thiochromen-4-ones **4**.

Table 2 One-pot three-component synthesis of 4*H*-thiochromen-4-ones **4**

Entry	Aroyl chloride **1**	Alkyne **2**	Product	Yield (%)
1	**1a**	**2a** R^2 = H [TMS]	**4a**	39
2	**1a**	**2b** $R^2 = C_6H_5$	**4b**	73
3	**1a**	**2c** $R^2 = 4\text{-}C_6H_4C(CH_3)_3$	**4c**	76
4	**1a**	**2d** $R^2 = 4\text{-}C_6H_4OCH_3$	**4d**	77
5	**1a**	**2e** $R^2 = 3,4\text{-}C_6H_3(OCH_3)_2$	**4e**	73
6	**1a**	**2f** $R^2 = 4\text{-}C_6H_4Cl$	**4f**	52
7	**1a**	**2g** $R^2 = {}^n$butyl	**4g**	59
8	**1a**	**2h** R^2 = ferrocenyl	**4h**	63
9	**1a**	**2i** R^2 = 6-methoxynaphthalen-2-yl	**4i**	51
10	**1c**	**2a** R^2 = H [TMS]	**4j**	35
11	**1c**	**2b** $R^2 = C_6H_5$	**4k**	61
12	**1c**	**2j** $R^2 = 4\text{-}C_6H_4CH_3$	**4l**	48
13	**1c**	**2c** $R^2 = 4\text{-}C_6H_4C(CH_3)_3$	**4m**	66
14	**1c**	**2e** $R^2 = 3,4\text{-}C_6H_3(OCH_3)_2$	**4n**	59
15	**1c**	**2k** $R^2 = 4\text{-}C_6H_4F$	**4o**	47

Table 3 Comparison of existing protocols for the synthesis of **4c**

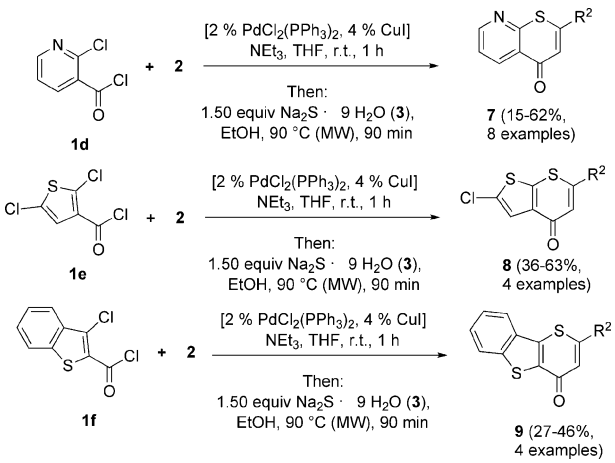
Route	Steps	Time	Yield (%)[a]
Wittig route[11]	3	~3 d	44
PPA[7]	2	~10 h	71
Propiolate route[5]	3	~4 d	34
CASNAR	1	~2 h	73

[a] Yield over all steps, starting from commercially available compounds.

The scope was then expanded to 2-chloronicotinoyl chloride (**1d**), 2,5-dichlorothiophene-3-carbonyl chloride (**1e**) and 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride (**1f**) as heteroaroyl chlorides, giving rise to the formation of the class of 4*H*-thiopyrano[2,3-*b*]pyridin-4-ones **7** (Scheme 4, Table 4), 2-chloro-4*H*-thieno[2,3-*b*]thiopyran-4-ones **8** and 7*H*-benzo-[*b*]thieno[3,2-*b*]thiopyran-7-ones **9** (Scheme 4, Table 5) in modest to moderate yields.

Since standard syntheses fail, to the best of our knowledge, only two examples of 4*H*-thiopyrano[2,3-*b*]pyridin-4-ones **7** have been reported in the literature prior to our studies.[21] 4*H*-thieno[2,3-*b*]thiopyran-4-ones **8** and 7*H*-benzo-[*b*]thieno[3,2-*b*]thiopyran-7-ones **9** are hitherto unknown heterocycles.

The structures of all annelated 4*H*-thiopyran-4-one derivatives **4**, **7**, **8** and **9** were unambiguously supported by spectroscopic (^1H, ^{13}C and DEPT NMR experiments, IR, UV/Vis, mass



Scheme 4 Coupling-addition-substitution (CASNAR) sequences to heteroaryl annelated 4*H*-thiopyran-4-ones **7**, **8** and **9**.

Table 4 One-pot three-component syntheses of 4*H*-thiopyrano[2,3-*b*]pyridin-4-ones **7** starting from 2-chloronicotinoyl chloride (**1d**)

Entry	Alkyne **2**	Product	Yield (%)
1	**2a** R^2 = H [TMS]	**7a**	62
2	**2b** $R^2 = C_6H_5$	**7b**	55
3	**2j** $R^2 = 4\text{-}C_6H_4CH_3$	**7c**	23
4	**2c** $R^2 = 4\text{-}C_6H_4C(CH_3)_3$	**7d**	15
5	**2f** $R^2 = 4\text{-}C_6H_4Cl$	**7e**	31
6	**2h** R^2 = ferrocenyl	**7f**	19
7	**2g** R^2 = *n*butyl	**7g**	17
8	**2l** R^2 = cyclopropyl	**7h**	53

spectrometry) and combustion analyses, and later by X-ray structure analyses for the compounds **4i** and **7h** (Fig. 1 and 2§).

Methodologically, this novel one-pot three-component CASNAR synthesis of annelated 4*H*-thiopyran-4-ones **4**, **7**, **8** and **9** proceeds efficiently under mild reaction conditions and with a broad variety of structurally and electronically diverse alkynes. Aliphatic, aromatic, heteroaromatic, and even ferrocenyl- or heteroatom-substituted alkynes can be successfully transformed in this reaction. If trimethylsilyl acetylene is applied, the TMS group is presumably lost during the Michael addition and the resulting 4*H*-thiopyran-4-one then bears a hydrogen atom at the R^2 position. Expectedly, free amino or hydroxy groups on the alkynes interfering with the electrophilic aroyl chloride reactivity should be protected. According to the substitution pattern of the compounds **4**, **7**, **8** and **9**, it becomes apparent that the electronic structure of substituent R^2 exerts the methodological limitation of the terminal Michael addition-S_NAr steps. Unfortunately, alkynones resulting from the coupling with alkoxy, acetal and electron poor aromatic substituents on the alkyne **2** were not successfully transformed into annelated 4*H*-thiopyran-4-ones.

Table 5 One-pot three-component syntheses of 2-chloro-4*H*-thieno[2,3-*b*]thiopyran-4-ones **8** and 7*H*-benzo-[*b*]thieno[3,2-*b*]thiopyran-7-ones **9**

Entry	Heteoaroyl chloride **1**	Alkyne **2**	Product	Yield (%)
1	**1e**	**2b** $R^2 = C_6H_5$	**8a**	40
2	**1e**	**2c** $R^2 = 4\text{-}C_6H_4C(CH_3)_3$	**8b**	63
3	**1e**	**2e** $R^2 = 3,4\text{-}C_6H_3(OCH_3)_2$	**8c**	51
4	**1e**	**2g** R^2 = *n*butyl	**8d**	36
5	**1f**	**2b** $R^2 = C_6H_5$	**9a**	46
6	**1f**	**2c** $R^2 = 4\text{-}C_6H_4C(CH_3)_3$	**9b**	41
7	**1f**	**2k** $R^2 = 4\text{-}C_6H_4F$	**9c**	27
8	**1f**	**2l** R^2 = cyclopropyl	**9d**	32

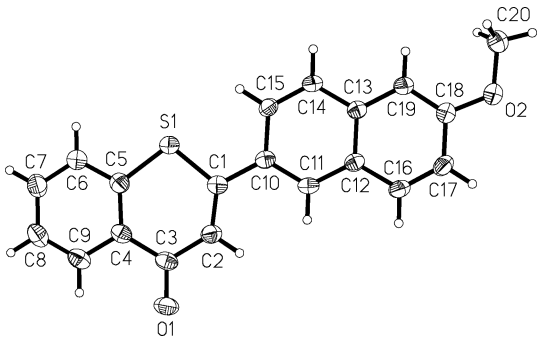


Fig. 1 X-Ray structure of **4i**.

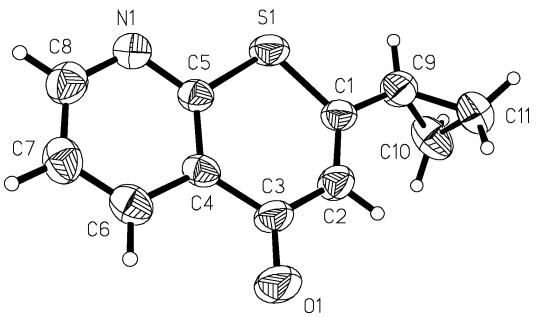


Fig. 2 X-Ray structure of **7h**.

Optical spectroscopy and electronic structure

Expectedly, UV/Vis absorption spectra of the annelated 4*H*-thiopyran-4-one derivatives **4**, **7**, **8** and **9** are quite similar (Table 6). For 4*H*-thiochromen-4-ones **4**, three distinct maxima $\lambda_{max,abs}$, appear in the spectra, whereas the longest wavelength band occurs at ~345 nm causing the bright yellow color of the compounds

§CCDC 745614 (**4i**) and CCDC 745615 (**7h**) contain supplementary crystallographic data for these structures. For crystallographic date in CIF or other electronic format see DOI: 10.1039/b917627f. Data were collected on a Bruker APEX diffractometer. Mo K_α radiation (λ = 0.71073 Å) was used in all cases, and the intensities were corrected for absorption effects using SADABS based on the laue symmetry of the reciprocal space. The structures were solved by direct methods and refined against F^2 with a full matrix least square algorithm using the SHELXTL software package. Hydrogen atoms were considered at calculated positions and refined using appropriate riding models. Relevant crystal and data collection parameters for the individual structures are given below. **Crystal data**: **4i**: $C_{20}H_{14}O_2S$, M = 318.38, monoclinic, space group $P2_1/n$, a = 13.6458(10), b = 5.7353(3), c = 19.9386(14) Å, β = 106.548(8)°, V = 1495.82(18) Å^3, T = 291(2) K, Z = 4, ρ = 1.414 g cm^{-3}, dimensions 0.60 × 0.35 × 0.12 mm^3, μ = 0.223 mm^{-1}, 0.3° omega-scans, 18 476 reflections measured, 2629 unique [R_{int} = 0.0826], 2629 observed [$I > 2\sigma(I)$], 209 parameters refined, goodness of fit 0.994, wR_2 = 0.0903, R_1 = 0.0444 (observed reflections), residual electron density –0.317–0.337 eÅ^{-3}, CCDC 745614. **7h**: $C_{11}H_9NOS$, M = 203.25, monoclinic, space group $P2_1/n$, a = 8.2503(9), b = 22.330(3), c = 10.694(2) Å, β = 103.40(3)°, V = 1916.5(5) Å^3, T = 291(2) K, Z = 8, ρ = 1.409 g cm^{-3}, crystal dimensions 0.30 × 0.30 × 0.30 mm^3, μ = 0.299 mm^{-1}, 0.3° omega-scans, 11 642 reflections measured, 3360 unique [R_{int} = 0.0983], 3360 observed [$I > 2\sigma(I)$], 1000 parameters refined, goodness of fit 0.848, wR_2 = 0.0469, R_1 = 0.0423 (observed reflections), residual electron density –0.157–0.252 eÅ^{-3}, CCDC 745615.

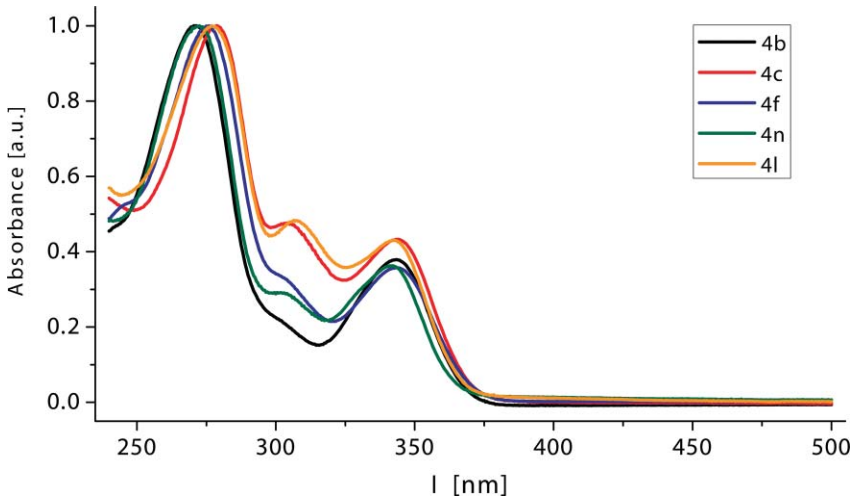


Fig. 3 Normalized UV/Vis spectra of selected 4*H*-thiochromen-4-ones **4** (recorded in CH_2Cl_2, $c_0 = 10^{-3}$ M; $T = 293$ K).

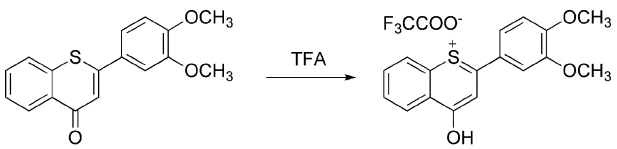
Table 6 UV/Vis data of annelated thiopyranones **4**, **7**, **8** and **9** (recorded in CH_2Cl_2, $c_0 = 10^{-4}$ M, $T = 293$ K)

Compound	λ_{max}/nm (ε/mol^{-1} L cm^{-1})
4a	249 (7300), 287 (2300), 337 (4400)
4b	272 (30900), 301 (6900), 344 (11700)
4c	280 (17300), 306 (8200), 345 (7500)
4d	265 (33700), 319 (31900), 342 (27700)
4e	255 (23000), 284 (11400), 339 (17700)
4f	277 (42700), 302 (14400), 345 (15300)
4g	249 (9600), 286 (1400), 337 (5500)
4h	260 (20600), 285 (18400), 307 (11900), 347 (9800), 389 (2200), 486 (1800)
4i	249 (22000), 329 (14600), 337 (16000)
4j	255 (24100), 337 (10700)
4k	272 (31600), 304 (8200), 343 (11000)
4l	279 (20100), 309 (9700), 343 (8700)
4m	278 (23400), 307 (11800), 343 (9800)
4n	259 (23300), 282 (11300), 341 (17100)
4o	273 (41900), 305 (12000), 343 (15100)
7a	249 (22000), 329 (14600), 337 (16000)
7b	269 (18700), 297 (10000), 345 (8800)
7c	274 (12300), 306 (10400), 345 (7300)
7d	274 (23800), 306 (21900), 345 (15400)
7e	271 (21200), 299 (14800), 343 (10100)
7f	263 (17400), 310 (14600), 345 (10400), 395 (2300), 493 (2200)
7g	252 (7800), 285 (2000), 335 (5700)
7h	259 (18700), 329 (9600), 338 (10500)
8a	277 (24500), 317 (8500)
8b	284 (23700), 316 (10200)
8c	254 (20900), 299 (19300), 325 (19700)
8d	248 (21600), 309 (12800)
9a	260 (21300), 286 (27500), 298 (26700), 307 (26600), 351 (13300)
9b	261 (9000), 287 (12400), 299 (13400), 308 (13900), 350 (6400)
9c	259 (25100), 286 (31500), 298 (30600), 308 (30900), 351 (15400)
9d	250 (17000), 259 (18600), 266 (15300), 276 (17600), 295 (15400), 305 (18400), 334 (10500), 347 (12000)

(Fig. 3). Depending on the substitution pattern, the second absorption band is not pronounced (~305 nm). The absorption band with the highest extinction coefficient is located at ~275 nm. This feature is characteristic for aromatic cores and can be assigned to substituents R^2.

Interestingly, all annelated 4*H*-thiopyran-4-one derivatives can be easily protonated upon addition of acids. Upon adding aliquots of trifluoroacetic acid to a solution of **4**, **7**, **8** or **9** in dichloromethane, a significant change in the absorption behavior of the compound occurred (Fig. 4).

Upon protonation, the $\lambda_{max,abs}$ value shifted from 345 to 370–440 nm. Interestingly, this was not a static phenomenon. Increasing aliquots of acid increased the bathochromic shifts, even visible with the naked eye—the color changed from yellow to orange. In addition, protonation caused orange luminescence ($\lambda_{max,em} = 460$ nm, see the ESI†) of the protonated heterocycle **4e-H$^+$**, with a fluorescence quantum yield lower than 1%, whereas the free base system **4e** was essentially nonluminescent. This pronounced bathochromic halochromicity of the absorption band can be rationalized by the generation of a cyanine-type push-pull system upon protonation. According to the HSAB principle,[22] protonation occurs preferentially at the harder carbonyl oxygen atom and not at the soft sulfur atom (Scheme 5).



4e **4e-H$^+$**

Scheme 5 Protonation of compound **4e** with trifluoroacetic acid.

This qualitative rationalization is also supported by DFT calculations (B3LYP/6-311G++)[23] on the thiopyranones and the corresponding related pyranones indicating a strongly zwitterionic character in the electronic ground state of the former (Fig. 5). The computations clearly show that the sulfur atom in the 4*H*-thiochromen-4-one structure possesses a significant positive partial charge of around +0.45 C, whereas the oxygen atom in the chromen-4-ones clearly has a negative partial charge of around –0.57 C. Compared to the natural product class of the flavones this connotes a complete inversion of the polarity of the ring system. The oxygen atoms of the carbonyl group in both systems expectedly display a negative partial charge of around –0.39 C.

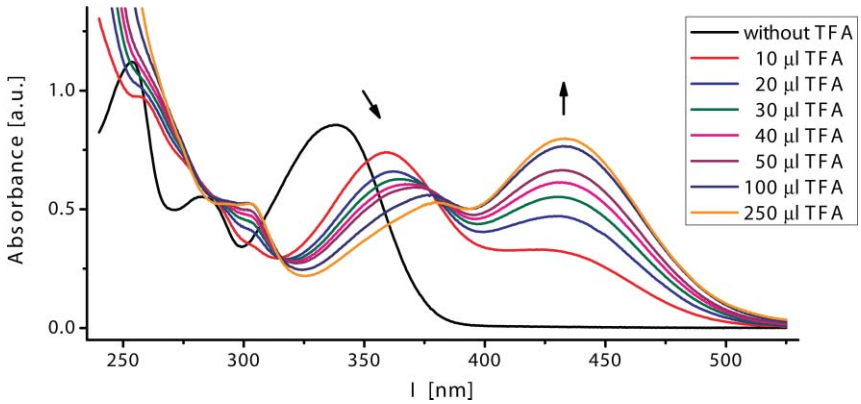


Fig. 4 Titration of **4e** with trifluoroacetic acid (recorded in CH_2Cl_2, $T = 298$ K).

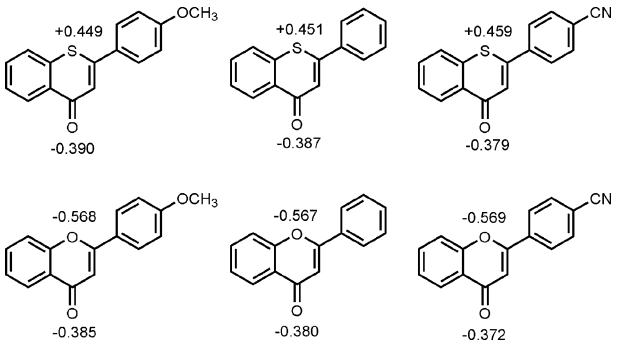


Fig. 5 DFT-computed charge distribution in selected thiochromenones (top row) and their flavone analogues (bottom row) (atomic partial charges are given).

Conclusions

The CASNAR sequence represents a straightforward and rapid method access to 4*H*-thiopyran-4-ones in the sense of a consecutive one-pot process and with a broad scope in the starting materials. Methoxy groups, which proved to be unfavorable in standard syntheses, are perfectly tolerated in this sequence. Furthermore, as a consequence of pronounced zwitterionic character of the computed electronic ground state, intense bathochromic halochromicity of the longest wavelength absorption bands with concomitant weak orange fluorescence can be observed upon protonation. This novel one-pot protocol now opens new avenues to related classes of annelated heterocycles. Studies addressing the detailed photophysics and the biological activity of 4*H*-thiopyran-4-ones are currently under investigation.

Experimental

All reactions involving water-sensitive compounds were carried out in flame-dried glassware under an argon atmosphere. Reagents and catalysts were purchased reagent grade and used without further purification. Solvents were dried by a solvent purification system. Flash column chromatography: silica gel 60, mesh 230–400. TLC: silica gel plates (60 F_{254}). ^{1}H, ^{13}C, DEPT, NOESY, COSY, HMQC and HMBC spectra were recorded with a 500 MHz NMR spectrometer using $CDCl_3$ as the solvent. The assignments of C_{quat}, CH, CH_2 and CH_3 were made on the basis of DEPT spectra. Mass spectra were recorded with a quadruple spectrometer. The melting points are uncorrected. IR spectra were taken on a FT-IR-spectrometer in KBr pellets and are reported in cm^{-1}. Elemental analyses were carried out in the microanalytical laboratory of the Pharmazeutisches Institut of the Heinrich-Heine-Universität Düsseldorf. Dielectric heating was performed in a single-mode microwave cavity (Discover Labmate, CEM GmbH, Kamp-Lintfort) producing continuous irradiation at 2450 MHz. The applied temperatures for microwave heating were held constant over the indicated reaction time by the implemented regulation system. Temperature and pressure as well as the cooling curve were monitored by the integrated controlling device.

General procedure for the synthesis of annelated 4*H*-thiochromen-4-ones 4, 7, 8 and 9

In a 10 ml microwave tube, $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol) and CuI (8 mg, 0.04 mmol) were dissolved in degassed THF (4 mL). Then, to this orange solution, acid chloride **1** (1.25 mmol), alkyne **2** (1.00 mmol) and triethylamine (1.05 mmol) were added. The reaction mixture was stirred at room temperature for 1 h. Finally, sodium sulfide nonahydrate (**3**) followed by ethanol (1 mL) were added to this suspension and the reaction mixture was heated at 90 °C in the microwave cavity for 90 min. After cooling to room temperature, the solvent was removed under reduced pressure and the crude products were purified by silica gel flash column chromatography (hexane/ethyl acetate) to afford the analytically pure 4*H*-thiochromen-4-ones **4**, **7**, **8** and **9** (for experimental details see the ESI, Tables 1–3†).

2-(4-Methoxyphenyl)-4*H*-thiochromen-4-one (4d)

Yellow solid, mp 97 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (s, 3 H), 7.01 (d, $^3J = 8.8$ Hz, 2 H), 7.20 (s, 1 H), 7.54 (ddd, $^3J = 8.2$ Hz, $^3J = 6.9$ Hz, $^4J = 1.3$ Hz, 1 H), 7.61 (ddd, $^3J = 8.2$ Hz, $^3J = 6.9$ Hz, $^4J = 1.3$ Hz, 1 H), 7.64-7.67 (m, 3 H), 8.54 (dd, $^3J = 8.1$ Hz, $^4J = 1.3$ Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5 (CH_3), 114.7 (2 CH), 122.2 (CH), 126.4 (CH), 127.6 (CH), 128.3 (2 CH), 128.5 (CH), 128.8 (C_{quat}), 130.9 (C_{quat}), 131.5 (CH), 137.6 (C_{quat}), 152.7 (C_{quat}), 161.9 (C_{quat}), 180.9 (C_{quat}). EI MS ($R_f = 20.3$ min, 70 eV, m/z (%)): 269 (19), 268 (M^+, 100), 267 (17), 240 (39), 225 (25), 197 (11), 136 (34), 132 (56), 120 (10), 117 (14), 108 (29), 89 (22), 69 (10), 63 (13). IR (KBr): $\tilde{\nu} = 1628$ cm^{-1} (s), 1605 (s), 1551 (w), 1509

(s), 1438 (w), 1336 (m), 1311 (w), 1269 (s), 1246 (w), 1184 (m), 1130 (w), 1117 (w), 1103 (w), 1020 (m), 862 (w), 831 (s), 798 (m), 774 (m), 732 (m), 666 (w), 623 (w), 568 (w), 517 (m). Anal. calcd for $C_{16}H_{12}O_2S$ (268.3): C 71.62, H 4.51; found: C 71.66, H 4.21%.

4*H*-Thiopyrano[2,3-*b*]pyridin-4-one (7a)

Yellow solid, mp 135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (d, ^3J = 10.6 Hz, 1 H), 7.50 (dd, ^3J = 8.1 Hz, ^3J = 4.5 Hz, 1 H), 7.93 (d, ^3J = 10.6 Hz, 1 H), 8.77 (dd, ^3J = 8.1 Hz, ^4J = 1.8 Hz, 1 H), 8.80 (dd, ^3J = 4.5 Hz, ^4J = 1.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 123.0 (CH), 126.1 (CH), 129.7 (C_{quat}), 136.9 (CH), 139.5 (CH), 152.7 (CH), 158.8 (C_{quat}), 180.6 (C_{quat}). EI MS (70 eV, *m*/*z* (%)): 164 (11), 163 (M^+, 100), 137 (18), 135 (28), 109 (11). IR (KBr): $\tilde{\nu}$ = 1625 cm^{-1} (s), 1579 (m), 1509 (w), 1450 (w), 1398 (s), 1366 (m), 1305 (w), 1265 (w), 1157 (w), 1072 (w), 842 (w), 791 (m), 717 (w), 670 (w). Anal. calcd for C_8H_5NOS (163.2): C 58.88, H 3.09, N 8.58; found: C 58.81, H 3.18, N 8.45%.

6-(4-^{t}Butylphenyl)-2-chloro-4*H*-thieno[2,3-*b*]thiopyran-4-one (8b)

Brown solid, mp. 157 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 9 H), 7.16 (s, 1 H), 7.51 (d, ^3J = 8.8 Hz, 2 H), 7.55 (d, ^3J = 8.8 Hz, 2 H), 7.57 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.1 (3 CH_3), 34.9 (C_{quat}), 124.1 (CH), 124.4 (CH), 126.4 (2 CH), 126.6 (2 CH), 131.0 (C_{quat}), 133.0 (C_{quat}), 137.2 (C_{quat}), 142.6 (C_{quat}), 151.5 (C_{quat}), 154.6 (C_{quat}), 175.7 (C_{quat}). EI MS (R_f = 32.0 min, 70 eV, *m*/*z* (%)): 336 (^{37}Cl-M^+, 32), 335 (12), 334 (^{35}Cl-M^+, 62), 321 (40), 320 (19), 319 (100), 290 (11), 263 (16), 207 (11), 179 (13), 178 (13), 177 (25), 176 (20), 148 (18), 147 (15), 146 (27), 128 (15), 127 (11), 115 (27), 69 (19). IR (KBr): $\tilde{\nu}$ = 2961 cm^{-1} (w), 1607 (s), 1508 (w), 1436 (w), 1414 (w), 1361 (w), 1271 (w), 1240 (w), 1114 (w), 1001 (w), 902 (w), 879 (w), 849 (w), 822 (w), 714 (w), 663 (w), 587 (w), 522 (w). Anal. calcd for $C_{17}H_{15}ClOS_2$ (334.9): C 60.97, H 4.51; found: C 60.80, H 4.60%.

6-Phenyl-4*H*-benzothieno[2,3-b]thiopyran-4-one (9a)

Beige solid, mp 157 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1 H), 7.49-7.53 (m, 4 H), 7.55–7.59 (m, 1 H), 7.68–7.70 (m, 2 H), 7.96–7.98 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 122.4 (CH), 132.7 (CH), 124.6 (CH), 125.2 (CH), 127.2 (2 CH), 128.6 (CH), 129.4 (2 CH), 130.8 (CH), 135.3 (C_{quat}), 136.1 (C_{quat}), 136.3 (C_{quat}), 137.3 (C_{quat}), 140.7 (C_{quat}), 152.1 (C_{quat}), 176.9 (C_{quat}). EI MS (70 eV, *m*/*z* (%)): 296 (12), 295 (20), 294 (M^+, 100), 266 (33), 192 (13), 164 (18), 133 (20), 120 (21), 40 (56). IR (KBr): $\tilde{\nu}$ = 1620 cm^{-1} (s), 1593 (s), 1544 (m), 1528 (w), 1499 (m), 1443 (m), 1345 (m), 1300 (m), 1242 (w), 1085 (m), 1052 (m), 951 (m), 864 (m), 753 (s), 727 (m), 684 (s), 578 (s). Anal. calcd for $C_{17}H_{10}OS_2 \cdot 1/8\ CH_2Cl_2$ (294.4 + 10.6): C 67.44, H 3.49; found: C 67.49, H 3.79%.

Acknowledgements

The authors gratefully acknowledge the Fonds der Chemischen Industrie and CEM for a research corporation.

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