RSC Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

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Cite this: *RSC Adv.*, 2020, **10**, 17427

Chlorotrifluoroethylidenes: an efficient and convenient approach to their synthesis†

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Received 17th March 2020
Accepted 15th April 2020

DOI: 10.1039/d0ra02481c

rsc.li/rsc-advances

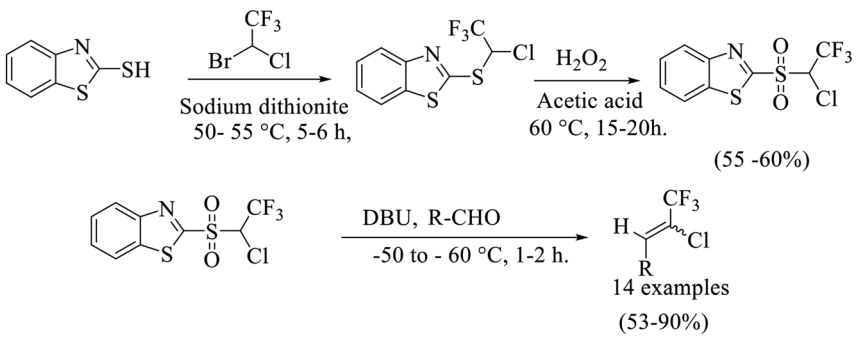
A convenient one step synthesis of chlorotrifluoroalkyl olefins starting from aldehydes was developed. The stable reagent 2-((1-chloro-2,2,2-trifluoroethyl)sulfonyl)benzothiazole was prepared from readily available benzothiazole-2-thiol and halothane. This method comprises using stable 2-((1-chloro-2,2,2-trifluoroethyl)sulfonyl)benzothiazole according to the Julia procedure and presents new opportunities for the synthesis of trifluoroalkylidene derivatives.

1. Introduction

The use of fluorinated compounds in medicinal chemistry, agrochemical fields and material science applications has had a remarkable impact on industrial and academic research. The presence of a fluorine (–F) or a trifluoromethyl ($-CF_3$) moiety often leads to improved lipophilicity, metabolic stability, bioavailability and binding selectivity.[1] Hence, the incorporation of a –F or $-CF_3$ group into organic compounds is a popular research area in organofluorine chemistry.[2]

The photo stable chlorotrifluoroethylidene (R–CH=$CClCF_3$) moiety, is an important structural unit which is present in pyrethroid insecticides.[3] The use of chlorotrifluoroethylidene was reported in the synthesis of various heterocycles containing a $-CF_3$ group such as substituted benzofurans.[4] The copper-catalyzed double thiolation reaction of 1,4-dihalides with sulfides has been reported for the selective synthesis of 2-trifluoromethyl benzothiophenes and benzothiazoles *via* chlorotrifluoroethylidene.[5] In addition, the synthesis of 1-aryl-3,3,3-trifluropropynes were reported using sodamide and the corresponding chlorotrifluoroethylidene.[5] Moreover, from the subsequent alkynes prepared from this alkylidine various heterocyles can be synthesize such as aryl trifluoromethyl-1,2,3-triazoles.[6–8] Various methods for the synthesis of chlorotrifluoroethylidenes have been reported in the literature (Scheme 1). The chlorotrifluoroethylidene group has been synthesized using aldehydes and CF_3CCl_2ZnCl, which was prepared from CF_3CCl_3 and zinc powder. However,

Julia reagent from halothane: a convenient one-step synthesis of chlorotrifluoroethylidenes



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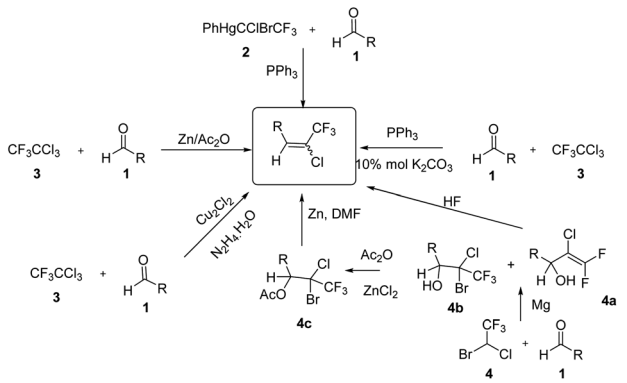
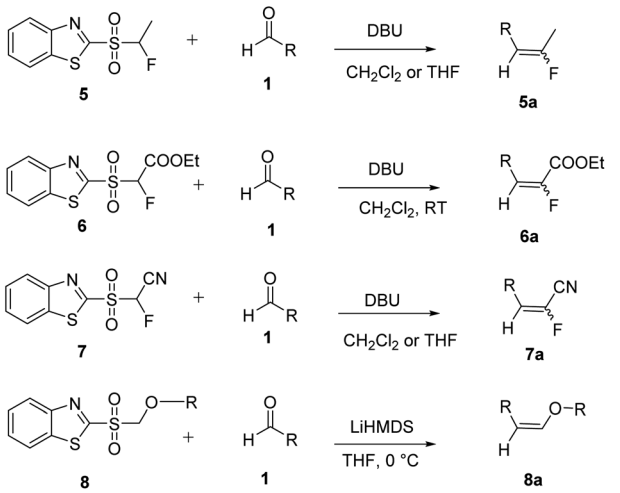


Scheme 1 Reported methods for synthesis of chlorotrifluoroethylidene derivatives.



Scheme 2 Benzothiazole based reagents for olefination reaction.

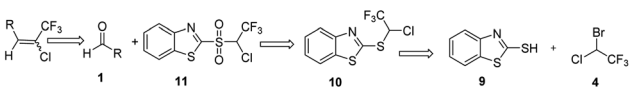
the selective formation of the chlorotrifluoroethylidene moiety requires an excess of zinc powder and acetic anhydride.[9] The most common method for the synthesis of chlorotrifluoroethylidene derivatives is the reaction of aldehydes or ketones with fluorinated phosphorous based reagents such as $PPh_3{=}CClCF_3$ or $(EtO)_2(O)PCClCF_3COOEt$. A major drawback of this approach is the difficulty in accessing their phosphoranes that requires an ozone depleting CFC reagent and which is not readily available.[10] The synthesis of chlorotrifluoroethylidene compounds was also reported using organomercury reagents. This procedure requires a high reaction temperature and a long reaction time (71 h).[11] A one-pot procedure was also reported for the synthesis of said alkene without isolation of the hydrazone by reacting the aldehyde with hydrazine hydrate followed by reaction with CF_3CCl_3 in the presence of copper(I) chloride.[8] Toshiyuki and co-workers reported the synthesis of chlorotrifluoroethylidene by reacting aldehydes with halothane under Grignard reaction condition (Scheme 1).[12] Hu and co-workers report a one-pot synthesis of chlorotrifluoroethylidene compounds using CF_3CCl_3 and triphenylphosphine.[13]

Julia and co-workers reported a one-step olefination reaction as an alternative to the HWE reaction.[14] According to this methodology the sulfone reacts with aldehydes or ketones to afford alkenes (Scheme 2). A number of synthetic applications of this reaction have been reported in the literature.[15–18] The selective preparation of fluoroalkenoates was reported using a modified Julia fluoroolefination.[19] Similarly the use of alkyl substituted-(1,3-benzothiazol-2-ylsulfonyl)fluoroacetates as reagents for the synthesis of substituted fluoroacrylates was reported (Scheme 2).[20] Various Julia olefination reactions have been reported in literature based on benzothiazole sulfones (Scheme 2).[21]

2. Results and discussion

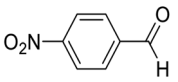
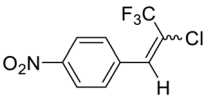
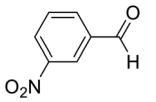
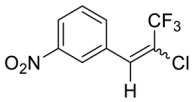
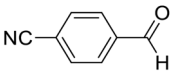
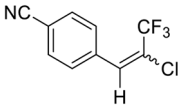
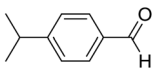
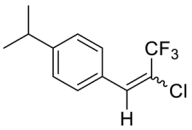
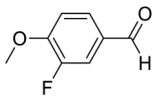
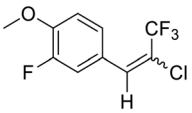
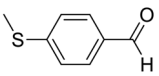
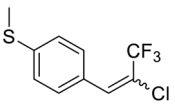
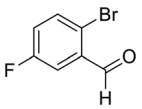
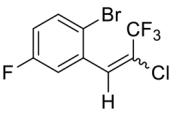
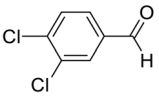
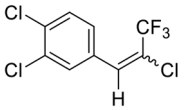
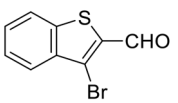
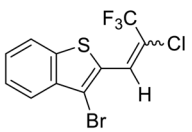
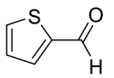
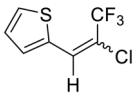
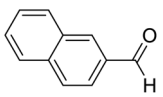
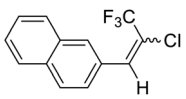
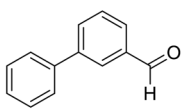
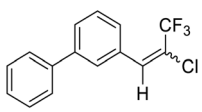
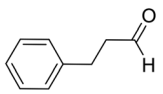
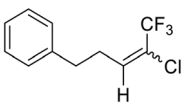
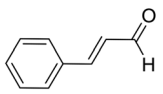
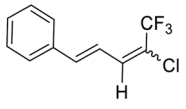
Based on the Julia olefination using benzothiazole sulfones a retro-synthetic analysis of the compound of interest *i.e.* chlorotrifluoroethylidene leads to the readily available materials benzothiazole-2-thiol and halothane (Scheme 3). Herein, we report a synthetic procedure for addition of chlorotrifluoromethyl group at the aldehyde using 2-((1-chloro-2,2,2-trifluoroethyl)sulfonyl)1,3-benzothiazole a sulfone reagent **11**. In an attempt to explore the scope and limitations of this methodology, a set of diverse aldehydes were reacted with sulfone reagent **11** in THF at −50 to −60 °C using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base to give the corresponding olefins in good to moderate yields (Table 1). 2-[(1-Chloro-2,2,2-trifluoroethyl)sulfanyl]-1,3-benzothiazole **10** was synthesized using the reported procedure, wherein 2-mercapto benzothiazole 9 was reacted with an excess of halothane **4** in DMF, in the presence of sodium bicarbonate and sodium dithionite at 55 °C.[22]

Various methods were investigated for the oxidation of the compound **10**. Oxidation with mCPBA in CH_2Cl_2 did not proceed to completion under varied reaction conditions such as the molar ratio, time and temperature. Oxidation using OXONE® and sodium bicarbonate in a THF/water mixture did not proceed to completion even with the use of 10 equiv. of OXONE®, leaving an unconverted monooxidized intermediate. Oxidation with H_2O_2 and acetic acid proceeded well but in low yield. Hence, further optimization of the reaction conditions such as temperature and the molar ratio of H_2O_2 were studied. It was observed that when to a solution of compound 10 (1.0 equiv.) in acetic acid (3 volumes), 50 wt% H_2O_2 solution (15–20 equiv.) was added in drop-wise manner at 60 °C resulted in completion of reaction in a good yield to afford compound **11**. The reaction mass was concentrated to 1 volume under vacuum and then ice water was added to precipitate the product sulfone **11**, which was isolated by filtration, post neutralization. Recrystallization of the sulfone from 3 volumes of IPA resulted

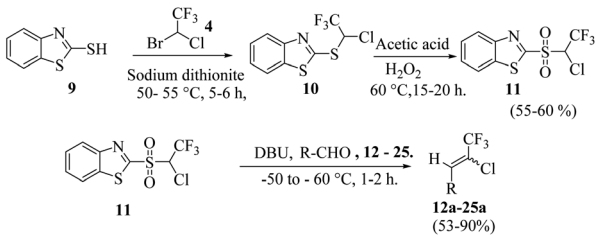


Scheme 3 Retro-synthesis of chlorotrifluoroethylidene derivatives.

Table 1 Olefination of various aldehydes using fluorosulfone **11**[a]

Entry no.	Substrate no.	Substrate	Product no.	Product	Yield (%)	*E* : *Z* ratio*
1	12		**12a**		80	81 : 19
2	13		**13a**		78	80 : 20
3	14		**14a**		82	65 : 35
4	15		**15a**		59	70 : 30
5	16		**16a**		73	64 : 36
6	17		**17a**		64	74 : 26
7	18		**18a**		84	92 : 8
8	19		**19a**		85	73 : 27
9	20		**20a**		92	49 : 51
10	21		**21a**		53	Na*
11	22		**22a**		85	76 : 24
12	23		**23a**		90	75 : 25
13	24		**24a**		80	70 : 30
14	25		**25a**		78	72 : 28

[a] Reagents and conditions: 11 (1.0 equiv.), DBU (2.1 equiv.), THF (15–20 w/v), −50 to −60 °C, RT, 1 h. *Relative ratio the of *E*/*Z* determined by ^{19}F NMR for the isolated compounds.



Scheme 4 Synthesis of chlorotrifluoroethylidene derivatives.

in the isolation of a white solid in 55–60% yield. Alternatively, it can be extracted in ethyl acetate post neutralization and column purified.

Lequeux and co-workers[19] have extensively studied the olefination of carbonyl compounds and reported the effect of various bases, temperature and solvent on the *E*/*Z* selectivity. In the optimization of reaction conditions for olefination of aldehydes *viz.* compound **12** with sulfone reagent **11**, among the different bases tried such as $CsCO_3$, LDA, NaHMDS, DBU and potassium tert-butoxide, only DBU gave the product in good yield in solvent THF at −50 to −60 °C (Scheme 4). The structure and configuration of the isolated compounds were confirmed by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. The assignment of *E*/*Z* isomers was done based on ^{19}F NMR δ values (*E* isomer δ value is −61 and *Z* isomer δ value is −67). ^{19}F NMR spectroscopy showed the "*E*" isomer as the major product. Compounds **12–14** (Table 1) containing electron-withdrawing groups on the aromatic ring gave good yields, as did halogen substituted compounds **18** and **19**. However, it was observed that electron-donating substituents on the aromatic ring such as compounds **15**, **16** and **17** resulted in low yields. This methodology also worked well for heterocyclic compound **20**; however, a low yield was obtained in the case of compound **21**. The naphathyl **22** and biphenyl **23** compounds also resulted in good yields of the corresponding olefins.

We then turned our attention towards the olefination of ketones. However, we found that this methodology under, the optimized conditions, did not work for ketones.[19] The selected compounds were 4-nitroacetophenone, 4-fluoroacetophenone, 4-methoxyacetophenone and benzophenone examined and that the reaction was unsuccessful. The sulfone reagent **11**, itself decomposed under the reaction conditions, as observed by TLC during reaction monitoring. The fact that the reaction failed for aromatic ketones is not clearly understood by us but may be due to a retroreaction as noted by Lequeux and co-workers.[14,19]

3. Conclusions

In conclusion, we have reported a method for the synthesis of R–CH=CClCF$_3$ compounds under mild conditions using a new benzothiazole sulfone halothane based reagent. This stable reagent is easy to synthesize from readily available starting materials. This method allows the preparation of a variety of chlorotrifluoroethylidene derivatives in moderate to good yields with the biggest advantage that it provides the "*E*" isomer as the major product compared to the Wittig methodology where the "*Z*" isomer is major product.

4. Experimental section

4.1. Procedure for preparation of 2-[(1-chloro-2,2,2-trifluoroethyl)sulfanyl]-1,3-benzothiazole (10)

2-Bromo-2-chloro-1,1,1-trifluoroethane (Halothane) (167.0 g, 847.7 mmol) was added dropwise to a stirred suspension of 1,3-benzothiazole-2-thiol **9** (50.0 g, 299 mmol), sodium bicarbonate (50.0 g, 595 mmol) and 85% sodium dithionite (104.0 g, 597 mmol) in 200.0 ml of DMF at 25 to 30 °C within 30 minutes. The reaction mixture was heated and stirred for 5–6 h at 55 °C. The reaction mass was poured into 200 ml water and extracted with 3 × 100 ml ethyl acetate. Combined organic layer was washed with water followed by brine and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and further purified by column chromatography to yield 2-[(1-chloro-2,2,2-trifluoroethyl)sulfanyl]-1,3 benzothiazole 58.3 g.

Yield: 69%; Pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): 8.12–8.09 (d, J = 9 Hz, 1H), 8.04–8.01 (d, J = 9 Hz, 1H), 7.57–7.54 (t, 1H), 7.52–7.43 (t, 1H), 7.26–7.19 (q, J = 6 Hz, 15 Hz, 1H) meets with reported compound; ^{19}F NMR(282.4 MHz, DMSO-d_6): −71.42 (s, CF_3, −3F) (reported −73.09 at 188 MHz in $CDCl_3$);[22] GC-MS (ESI 70 eV +ve) *m*/*z* 284 (M + 1), 283, 248, 228, 184, 166, 135, 122, 108, 69, 50; GC% purity 99.52%.

4.2. Procedure for preparation of 2-[(1-chloro-2,2,2-trifluoroethyl)sulfonyl]-1,3 benzothiazole (11)

H_2O_2 50 wt% solution (220 g. 3.23 mol) was added dropwise to a stirred solution of 2-[(1-chloro-2,2,2-trifluoroethyl)sulfanyl]-1,3 benzothiazole **10** (51.0 g 179.76 mmol) in acetic acid (160.0 2.67 mmol) over a period of 8 h at 60 °C. The completion of reaction is monitored by TLC. The reaction mass was concentrated to 1 volume under vacuum. The pH of the reaction mass adjusted to 8 to 7 using saturated sodium bicarbonate solution and product was extracted with ethyl acetate. The organic layer was washed with water followed by brine and dried over anhy-drous sodium sulphate. The solvent removed under vacuum and purified by column chromatography to yield 2-[(1-chloro-2,2,2-trifluoroethyl)sulfonyl]-1,3-benzothiazole 32 g.

Yield: 56%; white solid; mp 100–102 °C; ^{1}H NMR (300 MHz, DMSO-d_6): 8.47–8.42 (m, 1H), 8.41–8.34 (m, 1H), 7.84–7.80 (m, 1H), 7.79–7.74 (m, 1H), 7.62–7.55 (q, J = 6 Hz, 15 Hz, 1H);

^{13}C NMR (75 MHz, DMSO-d_6): 161.5 (Ar C, benzthiazole C, N=C–S, −1C), 152.4 (Ar C ring junction attached to nitrogen, −1C), 137.9 (Ar C ring junction attached to sulphur, −1C), 129.6, 129.0, 125.9, 124.2 (Ar C, −4C), 126.9, 123.2, 119.4, 115.7 (q, J_{CF} = 280.5 Hz, CF_3, −1C), 69.4, 69.0, 68.5, 68.1 (q, J_{CF} = 33.0 Hz, aliphatic C, Cl–C–CF3, −1C); 19F NMR (282.4 MHz, DMSO-d_6): −66.05 (s, CF_3, −3F); GC-MS (ESI 70 eV +ve) *m*/*z* 284 (M + 1), 315, 198, 170, 134, 117, 90, 69, 50; HRMS (ESI +ve) *m*/*z* $[M + H]^+$ calcd for $C_9H_6ClF_3NO_2S_2$: 315.9471, found 315.9475, *m*/*z* $[M + Na]^+$ $C_9H_5ClF_3NNaO_2S_2$: 337.9292, found 337.9294; GC% purity 94.1%.

4.3. Representative procedure for preparation of olefin

4.3.1. (*E*/*Z*)-1-(2-Chloro-3,3,3-trifluoroprop-1-en-1-yl)-4-nitrobenzene (12a). DBU (2 ml, 13.37 mmol) diluted in 5 ml THF was added to a stirred solution of sulfone **11** (2.0 g, 6.34 mmol) and 4-nitrobenzaldehyde 12 (0.957 g, 6.33 mmol) in 15 ml of THF at −50 to −60 °C slowly in 20 minutes. After addition the mixture was stirred for 1 h at −50 to −60 °C temperature. The reaction was then allowed to warm up to room temperature and stirred for a further 1 h. The completion of the reaction was monitored by TLC. The reaction mass was quenched with water. The aqueous layer was extracted with ethyl acetate 3 × 30 ml. The combined organic layer dried over sodium sulphate, filtered and evaporated under reduced pressure. The product was purified by column chromatography (silica, pet ether/AcOEt 95 : 5) to yield (*E*)-1-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-4-nitrobenzene **12a**. 1.28 g.

Mixture *E*/*Z* **12a**: yield: 80%; yellow oil; ^{19}F NMR (282.4 MHz, DMSO-d_6): −61.05 (s, CF_3, −3F, *E*−isomer), −67.70 (s, CF_3, −3F, *Z*-isomer); GC-MS (ESI 70 eV +ve) *m*/*z* 252(M + 1), 251, 221, 185, 169, 143, 120, 101, 75, 50 (similar fragments for both isomers-*E*/*Z* = 83.40 : 16.60); GC purity: 84.65%, RT – 33.85 min, *E*-isomer + 11.46% RT – 33.92 min, *Z*-isomer.

Pure *E* isomer of **12a**: yellow oil; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.29–8.28 (d, *J* = 3 Hz, 2H), 7.92 (s, 1H), 7.62–7.59 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 147.9 (Ar C attached to NO_2, −1C), 139.3(Ar C attached to olefinic bond –C=C, −1C), 137.5(3)–137.50 (Olefinc C attached to Ar ring –C=C, −1C), 130.1(4), 130.1(1) (Ar C meta to NO_2, −2C), 124.1, 123.9 (Ar C ortho to NO_2, −2C), 125.9, 122.2, 118.6, 115.0 (q, J_{CF} = 272.25 Hz, CF_3, −1C) 122.0, 121.5, 121.0, 120.5(5) (q, J_{CF} = 37.5 Hz, olefinic C, =C–CF_3Cl, −1C); GC-MS (ESI 70 eV +ve) *m*/*z* 252(M + 1), 251, 221, 185, 169, 143, 120, 101, 75, 50; GC purity: 99.65% (RT – 33.85 min, *E*-isomer).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are thankful to Madhusudan Sarwate and Sachin Kakale from Navin Fluorine International Limited, India for their support in recording spectroscopic data. The authors are also thankful to Dr Owen Chambers and Dr G. S. K Surya Prakash for their valuable guidance.

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