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A Highly Efficient Approach for the Synthesis of Novel Trifluoroacetylated Enaminones using DBU as a Base

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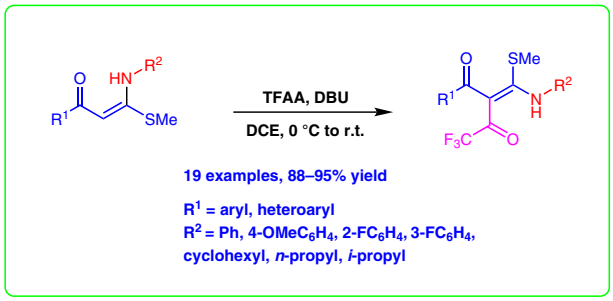

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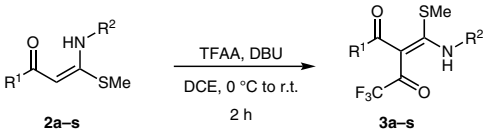
Abstract An efficient methodology has been developed for the synthesis of a variety of novel trifluoroacetylated enaminones by using trifluoroacetic anhydride in DCE as solvent and DBU as a base via electrophilic trifluoroacetylation. X-ray crystallographic studies confirmed the trifluoroacetylation and *E* stereoisomeric form of the novel compounds. The synthetic strategy has the advantage of using an inexpensive and non-toxic base for producing excellent yields. Synthons bearing variety of functional groups may be further extended for the formation of heterocyclic compounds.

Keywords trifluoroacetylation, electrophilic, enaminones, trifluoroacetic anhydride, DBU

Development of new methodologies for the synthesis of fluorine-containing compounds is of great interest due to their importance in pharmaceuticals,[1] polymers[2] and agrochemicals.[3] Among them, trifluoroacetylated compounds are of significant interest as pesticides.[4,5] Incorporation of the trifluoroacetyl group can increase solubility, binding site interaction and hydrophobicity.[6] A survey of the literature reveals various methods for trifluoroacetylation, using pyridine as base.[7] However, due to the problem of environmental hazards and toxicity,[8] it is desirable to replace the pyridine with a less toxic, non-hazardous base. Thus, we have concentrated on the development of new and efficient synthetic methods for trifluoroacetylation. DBU is very interesting as it can be used as an efficient base.[9]

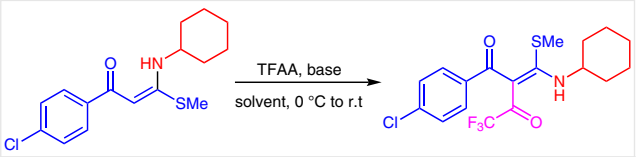
Enaminones are versatile synthons for the synthesis of various heterocyclic compounds[10] because the olefinic linkage is activated by electron-releasing alkylthio and amino groups through p–π conjugation. This makes it reactive towards electrophiles such as trifluoroacetic anhydride to afford trifluoroacetylated enaminones.[11] These synthons could serve as useful building blocks in the construction of functionalized heterocycles[12,13] bearing a trifluoromethyl or trifluoroacetyl group. However in spite of their wide scope of application, enaminones have not been heavily exploited in trifluoroacetylation reactions and there is only scanty information available on these important synthons.[11] In continuation of our research interest in enaminones,[14–16] we report herein an efficient synthesis of trifluoroacetylated synthons, by using the non-toxic and non-hazardous base DBU.

The enaminones **2a–s** were easily prepared by direct amination from α-oxoketene dithioacetals[15] and substituted amines by refluxing in toluene.[17] Compounds **2a–s** were isolated as single *E* stereoisomers as previously reported.[14] Compounds **3a–s** were efficiently synthesized[18] from enaminones **2a–s** by using TFAA in the presence of DBU as a base at room temperature (Scheme 1).



Scheme 1 Synthesis of trifluoroacetylated enaminones

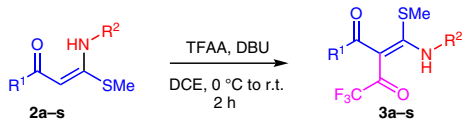
The optimized reaction conditions were established by attempting a model reaction for the synthesis of **3l** (Scheme 2). The reaction was screened using various solvents, bases and by varying time of the reaction for the synthesis of (*E*)-1-(4-chlorophenyl)-2-[(cyclohexylamino)(methylthio)-methylene]-4,4,4-trifluorobutane-1,3-dione (**3l**) from (*E*)-1-(4-chlorophenyl)-3-(cyclohexylamino)-3-(methylthio)prop-2-en-1-one (**2l**). First, we carried out the reaction with TFAA in $CHCl_3$ in the presence of DBU as base at room temperature. The progress of the reaction was monitored by TLC and was found to be complete after two hours and **3l** was obtained in 74% yield after workup (Table 1, entry 1).



Scheme 2 Screening of optimal reaction conditions for **3l**

The above reaction was then carried out using carbon tetrachloride, dichloromethane and dichloroethane as solvents under identical conditions. The reactions were complete in 2–3 hours and gave 75%, 73% and 94% yield of product **3l**, respectively (Table 1, entries 2–4). The same reaction was then explored in tetrahydrofuran, acetonitrile under similar conditions. The reaction was found to be complete in six hours and seven hours and gave 62% and 65% yields of the desired product **3l**, respectively (Table 1, entries 5 and 6). As the best results were obtained when the reaction was attempted in DCE, it was chosen for further exploration of this reaction. To determine the effect of bases other than DBU, the reaction was attempted using DABCO, triethylamine, diethylamine and DIPEA in DCE at room temperature. The reactions were found to be complete in 3–4 hours and gave **3l** in 86%, 40%, 42%, and 70% yields, respectively (Table 1, entries 7–10). Then same reaction was repeated with inorganic bases, sodium carbonate, potassium carbonate and cesium carbonate, but the desired product was only formed in 40–42% yield even after running the reaction for eight hours (entries 11–13). When we carried out the reaction of **2l** with TFAA in the absence of base, no product was obtained (Table 1, entry 14). The effect of reagent amount on the reaction time and yield of the product was also examined. There was no significant effect on the product yields under these conditions (Table 1, entries 15 and 16). Thus, on the basis of these observations, the optimal reaction conditions for the synthesis of **3l** were established to be DBU in DCE at room temperature for two hours.

With the optimal conditions in hand, we next turned our attention to explore the substrate scope by testing various enaminones **2a–s**, and the results are summarized in Table 2. All the reactions were complete in less than three hours with both electron-rich and electron-deficient enaminones affording the desired products **3a–s** in high yields (Scheme 3). When unsubstituted phenyl rings were present on both sides, product **3a** was obtained in 90% yield (Table 2, entry 1). When R^1 and R^2 bore electron-rich or electron-deficient phenyl groups, enaminones **2b–g** were transformed smoothly into the desired products **3b–g** in 88–92% yield (Table 2, entries 2–7). A yield of 89% was obtained



Scheme 3 Substrate scope of the synthesis of novel trifluoroacetylated enaminones

Table 1 Preparation of Trifluoroacetylated Enaminones

Entry	Solvent	Base	Reagent TFAA (equiv)	Temp. (°C)	Time (h)	Yield (%)[b]
1	$CHCl_3$	DBU	2.5	r.t.	2	74
2	CCl_4	DBU	2.5	r.t.	3	75
3	CH_2Cl_2	DBU	2.5	r.t.	3	73
4	**DCE**	**DBU**	**2.5**	**r.t.**	**2**	**94**
5	THF	DBU	2.5	r.t.	6	62
6	MeCN	DBU	2.5	r.t.	7	65
7	DCE	DABCO	2.5	r.t.	3	86
8	DCE	TEA	2.5	r.t.	4	40
9	DCE	DEA	2.5	r.t.	4	42
10	DCE	DIPEA	2.5	r.t.	4	70
11	DCE	Na_2CO_3	2.5	r.t.	8	42
12	DCE	K_2CO_3	2.5	r.t.	8	40
13	DCE	Cs_2CO_3	2.5	r.t.	8	42
14	DCE	–	2.5	r.t.	8	–
15	DCE	DBU	2	r.t.	3	88
16	DCE	DBU	3.5	r.t.	2	90

[a] Reaction conditions: **2l** (1.0 equiv), DBU (2 equiv), TFAA (2.5 equiv), DCE, reaction at 0 °C to r.t.
[b] Isolated yield.

with a cyclopropyl group present as R^1 (entry 8). Moreover when heteroaryl groups were present as R^1, **3i**, and **3j** were furnished in 88% and 87% yield, respectively (Table 2, entries 9 and 10). Substrates with an electron-deficient aromatic substituent R^1 and a cyclohexyl group as R^2 gave intriguing trifluoroacetylated products **3k–m** in 94–95% yield (Table 2, entries 11–13); whereas substrates with R^1 containing electron-donating groups (4-MeC_6H_4 or 4-$OMeC_6H_4$) and a cyclohexyl group as R^2 gave yields of 90% and 88%, respectively (Table 2, entries 14 and 15). However a yield of 90–95% was observed when isopropyl and *n*-propyl groups were present as R^2 (Table 2, entries 16–19).

Table 2 Synthesis of Novel Trifluoroacetylated Enaminones

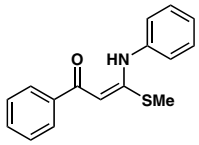
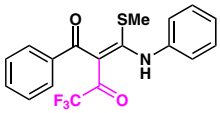
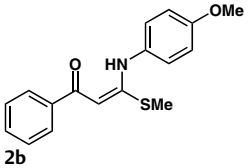
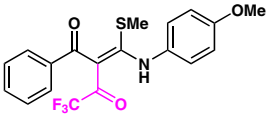
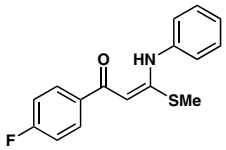
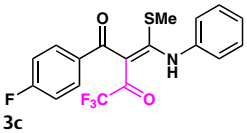
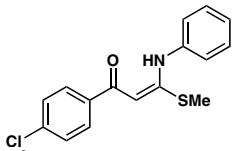
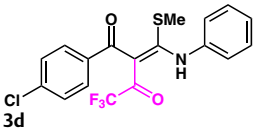
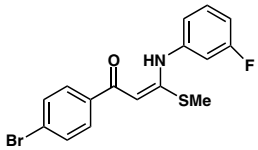
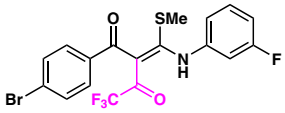
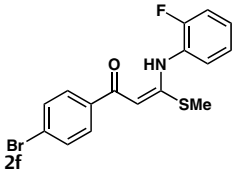
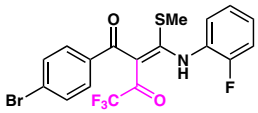
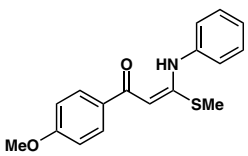
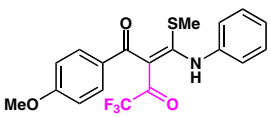
Entry	Substrate	Product	Yields (%)
1	 **2a**	 **3a**	90
2	 **2b**	 **3b**	92
3	 **2c**	 **3c**	92
4	 **2d**	 **3d**	90
5	 **2e**	 **3e**	88
6	 **2f**	 **3f**	89
7	 **2g**	 **3g**	89

Table (continued)

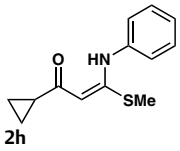
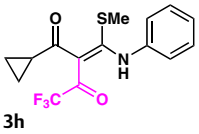
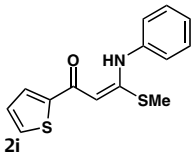
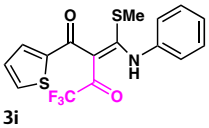
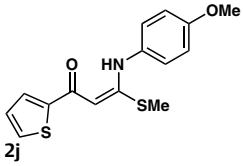
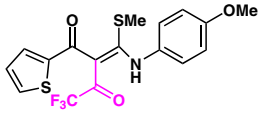
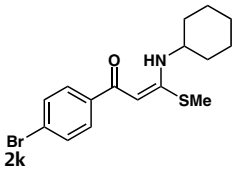
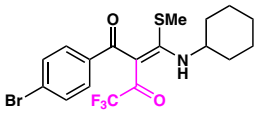
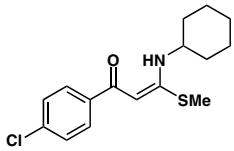
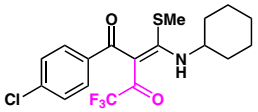
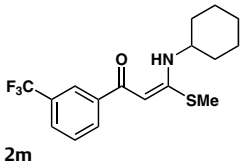
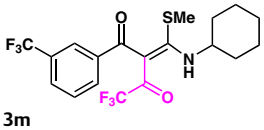
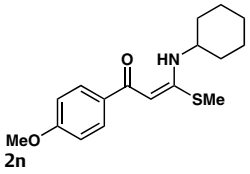
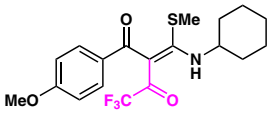
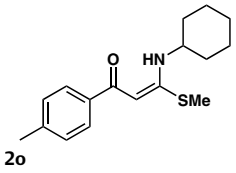
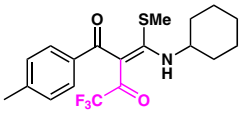
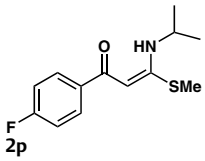
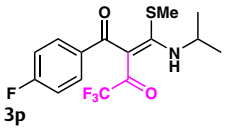
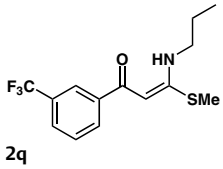
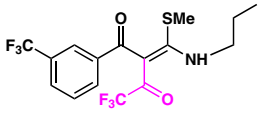
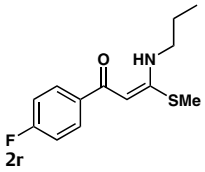
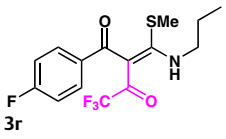
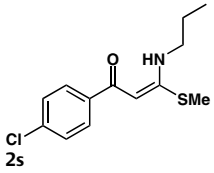
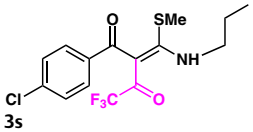
Entry	Substrate	Product	Yields (%)
8	 **2h**	 **3h**	89
9	 **2i**	 **3i**	88
10	 **2j**	 **3j**	87
11	 **2k**	 **3k**	95
12	 **2l**	 **3l**	94
13	 **2m**	 **3m**	95
14	 **2n**	 **3n**	90
15	 **2o**	 **3o**	88

Table (continued)

Entry	Substrate	Product	Yields (%)
16	 **2p**	 **3p**	90
17	 **2q**	 **3q**	95
18	 **2r**	 **3r**	95
19	 **2s**	 **3s**	94

Structural assignments of **3l** were made on the basis of IR, ^{1}H, ^{13}C, ^{19}F NMR and HRMS data. Disappearance of the vinylic peak at δ = 5.49 ppm was observed in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum of compound **3l**, displacement of the peak corresponding to the olefinic carbon at δ = 85.55 ppm with simultaneous appearance of a peak at δ = 174.01 ($COCF_3$), 115.88 ($COCF_3$) and 107.74 (=$\underline{C}COCF_3$) ppm confirmed the incorporation of a trifluoroacetyl group at the olefinic position. In the ^{19}F NMR spectrum, appearance of a peak at δ = –70.68 ppm confirmed the presence of a trifluoromethyl group. HRMS data of the **3l** compound showed the [M + 1] peak at *m*/*z* = 406.0853. An X-ray crystallographic study of compound **3q** confirmed the single *E*-stereoisomeric form of the final product (Figure 1).

In conclusion, a convenient and efficient strategy has been developed for the synthesis of novel trifluoroacetylated enaminones using DBU as base. The easy accessibility of the starting materials, simplicity of execution and mild reaction conditions make this strategy convenient. The conditions tolerate a wide variety of functional groups which can be further extended for the synthesis of heterocycles such as pyrazoles, pyrimidines or benzodiazepines.

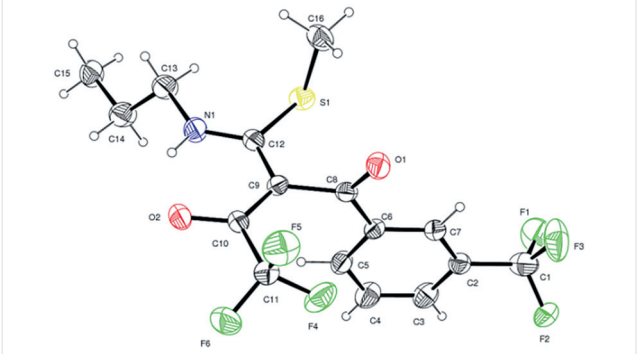


Figure 1 ORTEP diagram of **3q** (CCDC 1515192)

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588865.

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(18) **General Procedure for the Synthesis of Trifluoroacetylated Enaminones 3a–s**: To a solution of enaminones **2a–s** (1 equiv) in DCE (5 mL) was added DBU (2 equiv) under a N_2 atmosphere. TFAA (2.5 equiv) was added dropwise over 10 min, keeping the temperature at 0 °C. When addition was complete, the mixture was allowed to warm slowly to r.t. and stirred for 2 h, monitoring by TLC. After completion of the reaction, the mixture was quenched with aq $NaHCO_3$, then washed with dilute HCl and finally H_2O. The mixture was extracted with CH_2Cl_2 and the organic layer was dried over anhyd Na_2SO_4. After filtering and concentrating by rotary evaporation, a solid product was obtained that was crystallized from Et_2O–pentane (5%) to give the pure compounds **3a–s**.

(*E*)-1-(4-Chlorophenyl)-2-[(cyclohexylamino)(methylthio)methylene]-4,4,4-trifluorobutane-1,3-dione (3l): The compound was obtained as a white solid; mp 108–110 °C; yield: 0.36 g (94%). IR (KBr): 3448, 2933, 1726, 1654, 1574, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.07 (br s, 1 H, NH), 7.75 (t, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 3.95 (s, 1 H, NHC*H*), 2.19 (s, 3 H, SMe), 1.87–1.90 (m, 3 H), 1.72–1.74 (m, 2 H), 1.55–1.57 (m, 1 H), 1.24–1.46 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.17, 174.01 (*C*OCF_3), 167.94, 139.44, 137.82, 130.57, 128.83, 128.64, 128.44, 118.75, 115.88 (*C*OCF_3), 107.74 (=*C*$COCF_3$), 55.21, 33.36, 24.95, 24.16, 19.43 (SMe). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.68 (s, 3 F, $COCF_3$). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}ClF_3NO_2S$: 406.0855; found: 406.0853.

(*E*)-4,4,4-Trifluoro-2-1-(4-chlorophenyl)-2[(methylthio)(propylamino)methylene]-1-[3-(trifluoromethyl)phenyl]butane-1,3-dione (3q): The compound was obtained as a white solid; mp 60–62 °C; yield: 0.37 g (95%). IR (KBr): 3418, 2903, 1723, 1621, 1562, 1464 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.95 (br s, 1 H, NH), 8.06 (s, 1 H), 7.99 (d, *J* = 7.6 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 7.54 (d *J* = 7.6 Hz, 1 H), 3.58 (q, *J* = 6.1 Hz, 2 H), 2.15 (s, 3 H, SMe), 1.65–1.74 (m, 2 H), 1.00 (t, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.76, 174.42 (*C*OCF_3), 169.21, 140.03, 132.26, 129.21, 128.08, 125.77, 115.78 (*C*OCF_3), 107.67 (=*C*$COCF_3$), 48.06, 23.14, 18.48 (SMe), 11.29 (Me). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.73 (s, 3 F, $ArCF_3$), –71.87 (s, 3 F, $COCF_3$). HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}F_6NO_2S$: 400.0806; found: 400.0801.