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TRIFLUOROMETHYLSULFENYLATION OF MASKED CARBONYL COMPOUNDS

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Abstract: Incorporation of fluorine and fluorine containing groups such as trifluoromethyl and trifluoromethylthio moieties considerably enhances the biopharmacological properties of the parent precursors. Trifluoromethylsulfenylation of masked carbonyl functions, such as the enamines using N-(trifluoromethylthio)phthalimide is described in this communication.

Since the presence of the SCF_3 group profoundly enhances the biological activity of the precursors[1], considerable interest has manifested in the chemistry of this functional group.[2] The synthesis of triflouromethylthiocopper in pure crystalline form[3a] as well as its X-ray crystallographic structure determination[3b] have been described. However, this reagent can not be used in the preparation of α-trifluoromethylthiolated carbonyl compounds. The search for an efficient trifluoromethylthiolating agent has led us to explore the reaction of N-(trifluoromethylthio)phthalimide. Mild reaction conditions of the enamine

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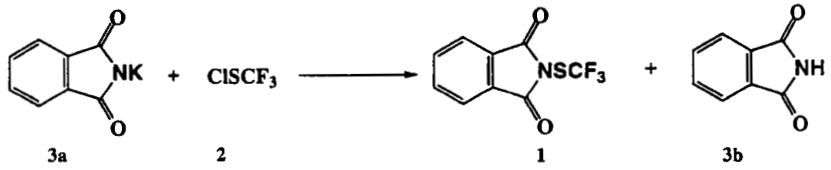
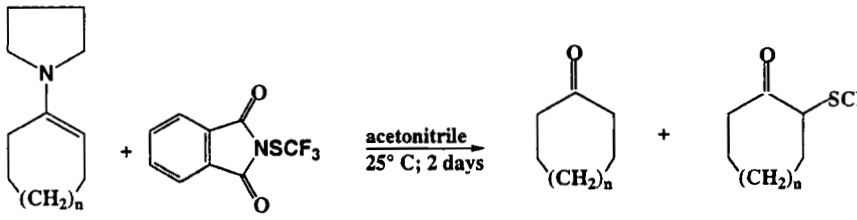
preparation, the regiospecific C-alkylation and facile regeneration of the α-substituted carbonyl compounds have all combined to make enamines a versatile group of intermediates.[4,5] Enamines readily react with electrophiles to give mono- and disubstituted products and the involved mechanistic considerations have been amply discussed.[4,6] Trifluoromethylsulfonate yields α–(trifluoromethylsulfonyl)-cyclohexanone from cyclohexenylenamine[7a], while the latter reacts with benzoyl peroxide to yield α–carbonyl benzoates.[7b] While enamines with N-fluoro-2-pyridone gave α-fluorocarbonyl derivatives[8a], direct fluorination of cyclohexenyl-enamine furnished poor yields of mono- and difluorocyclohexanones.[8b] The reaction of enamines with trifluoromethylsulfenyl chloride itself yields a complex mixture of compounds.[9a] A similar type of product formation, in which the pyrrolidine part was still attached to the product and the cyclohexene ring had been aromatized to the phenyl moiety has been reported.[9b] Whereas the trifluoromethylthiolation of enamine derivatives with N-(trifluoromethylthio)-phthalimide primarily furnishes α-trifluoromethylthiolated carbonyl compounds (>85% yield), reactive methylene compounds such as ethyl acetoacetate (**10**) and diethyl malonate (**12**) fail to react with N-(trifluoromethylthio)phthalimide (Scheme 1). This failure even at elevated temperature to trifluoromethylthiolate carbonyl compounds containing the reactive methyene groups with N-(trifluoromethylthio)-phthalimide has a precedent.[9c] While the reaction of enamines with N-(trifluoromethylthio)phthalimide gives satisfactory yields of α–trifluoromethylthio-lated carbonyl compounds in a clean process, the reaction of enamines with trifluoromethylsulfenyl chloride yields a complex mixture of compounds.[9a]



3a 2 1 3b

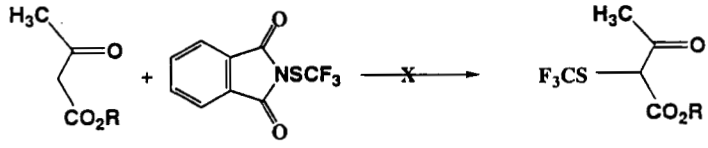


4: n=1
7: n=0

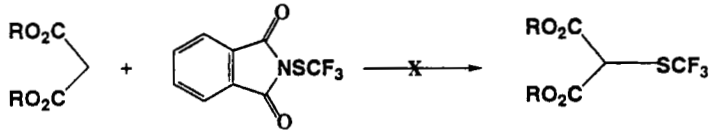
1

5: n=1
8: n=0

6: n=1
9: n=0



10: R=C_2H_5 1 11: R=C_2H_5



12: R=C_2H_5 1 13: R=C_2H_5

Scheme 1

Experimental

Trifluoromethylsulfenyl chloride is extremely toxic and corrosive. Hence, extreme care and caution should be exercised while working with it. All solvents were dry and freshly distilled prior to use. The reactions were carried out in a flame-dried, argon gas-purged 10 or 25 ml three-necked flask equipped with a magnetic stirrer, gas inlet-adaptors and a reflux condenser carrying a dry ice/ acetone cooled trap. The temperature of the coolant passing through the condenser was maintained at -20 °C. All reactions were carried out by addition of stoichiometric amounts trifluoromethylsulfenyl chloride via the vacuum line to the substrate cooled to -78 °C. The reaction mixture was initially analyzed by GC and GC-MS, then the solvent was evaporated under reduced pressure and the residue was vacuum distilled and again analyzed by GC/MS. Mass spectra were obtained on a Finnigan Model 5100 GC/MS equipped with a silica 25 m x 0.31 mm. i.d. SE-54 capillary column (J and W Scientific, Rancho Cordova, CA). Routine GC analyses were accomplished with a Hewlett-Packard 5890A gas chromatograph equipped with a J and W Scientific 30 m x 0.53 mm i.d. DB-5 column (J and W Scientific, Folsom, CA). The NMR spectra (^{1}H, ^{13}C and ^{19}F) were recorded in $CDCl_3$ with TMS as the internal standard on a Varian VXR-400S spectrometer at 100 MHz and 376 MHz respectively. The external reference for ^{19}F was CCl_3F.

Synthesis of N-(trifluoromethylthio)phthalimide (**1**): Trifluoromethylsulfenyl chloride (**2**) was introduced via the vacuum line through a suspension of potassium phthalimide (**3a**) at - 0° C. After the suspended salt had dissolved, the reaction mixture was heated for seven hours at 90-100° C with the coolant circulating through the reflux condenser was kept at -20° C. The reaction mixture was cooled to room temperature, filtered and solvent evaporated under reduced pressure. The solid residue consisted of phthalimide (**3b**) and N-(trifluoromethylthio)phthalimide

(**1**). Recrystallization of the solid from acetone gave essentially pure N-(trifluoromethylthio)phthalimide (**1**), m.p.115-117°.[10]

Mass spectral fragmentation of N-(trifluoromethylthio)phthalimide (**1**): M^+ = 247 (100%); 228 (M-F); 219 (M-CO); 203 (219-O); 178 (M-CF_3); 162 (178-O); 150 (M-CF_3-CO); 132 (M-$NSCF_3$); 122 (150-CO); 104 (C_6H_4CO); 101 (SCF_3); 90 (CO_2NS); 76 (C_6H_4); 69 (CF_3); 50 (CF_2), 46 (NS); and 32 (S).

Trifluoromethylthiolation of Pyrrolidino-1-cyclohexene (**4**): A stochiometric quantity of N-(trifluoromethylthio)phthalimide (**1**, 0.78 g., 0.005 mole) was added to a solution of pyrrolidino-1-cyclohexene (**4**, 0.75 g., 0.005 mole) in 15 ml of freshly distilled dry acetonitrile under argon at room temperature and with stirring. It was stirred for two days at room temperature. The reaction mixture was treated with a dilute solution of hydrochloric acid, extracted with ether, the extract was successively washed with water and saturated solution of sodium chloride, dried over anhydrous sodium sulfate and solvent evaporated under reduced pressure. The GC analysis of the residue showed the presence of two compounds. The GC-MS analysis of the reaction product confirmed the above observation and enabled the structure elucidation of the two compounds, namely cyclohexanone (**5**, 0.08 g., 12%) and 2-(trifluoromethylthio)cyclohexanone (**6**, 0.75 g., 87.8%).

Mass spectral fragmentation of 2-(trifluoromethylthio)cyclohexanone (**6**): M^+= 198; 170 (M-CO or M-C_2H_4); 101 (100%, SCF_3); 97 (M-SCF_3); 82 (CSF_2); 69 (CF_3); 63 (CSF); 55 (C_3H_3O); 45 (CSH); 41 (C_3H_5) and 27 (C_2H_3).

Reaction of pyrrolidino-1-cyclopentene (**7**) with N-(trifluoromethylthio)phthalimide (**1**): Stoichiometric amounts 1-pyrrolidino-1-cyclopentene (**7**, 0.68 g., 0.01 mole) and N-(trifluoromethylthio)phthalimide (**1**,0.78 g., 0.01 mole) were dissolved in dry acetonitrile and stirred at room temperature for two days under

argon. The reaction mixture was quenched with a saturated solution of ammonium chloride, extracted with methylene chloride, organic extract separated from the aqueous layer, successively washed with dilute HCl, water and saturated solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. GC-MS-CI analysis of the residue indicated the presence of two compounds in reaction mixture: (a) cyclopentanone (**8**, 0.05 g., 12.9%) and (b) 2-(trifluoromethylthio)cyclopentanone (**9**, 0.8 g., 87.1%). Cyclopentanone (**8**) resulted from the hydrolysis of the starting enamine, namely **7**. The structure of 2-(trifluoromethylthio)cyclopentanone (**9**) was further confirmed by GC-MS-EI analysis.

Mass spectral fragmentation of 2-(trifluoromethylthio)cyclopentanone (**9**): M^+=184, 156 (M-CO), 141 ($C_3H_4SCF_3$), 128 ($C_2H_3SCF_3$), 115 (M-CF_3), 101(SCF_3), 99 (C_5H_7S), 87 (C_3H_3OS, 100%), 83 (M-SCF_3), 73 (C_3H_5S), 69 (CF_3), 59 (C_2H_3S), 55 (C_3H_3O), 45 (CSH), 42 (C_3H_6), 39 (C_3H_3), and 27 (C_2H_3).

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