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Efficient synthesis of novel 9*H*-xanthen-9-yl derivatives of bidentate heterocyclic nucleophiles by $Fe(HSO_4)_3$ as a catalyst

Hossein Eshghi *, Mehdi Bakavoli, Javad Abedini-Torghabeh, Mohammad Rahimizadeh

Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, P.O. Box 91775-1436, Mashhad, Iran

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Abstract

We have demonstrated the direct substitution of 9*H*-xanthen-9-ol with different nucleophilic reagents such as thiazoles, triazoles, tetrazoles, hydrazines and hydrazinecarboxamides in good to high yields. This reaction catalyzed by ferric hydrogensulfate as a heterogeneous acid catalyst in ethanol through S_N1 type reaction of pyrylium with a nucleophilic reagent afforded the heterocycle- and aromatic-*N*-substituted xanthene derivatives as simple marked molecules in short reaction times.

Keywords: Xanthen; Ferric hydrogensulfate; Nucleophilic reagents; S_N1 type

9*H*-Xanthen-9-ol falls in the group of non-specific reagents since it reacts with various natural products, urea, amino acids, ribonuclease and cytochrome [1], 9*H*-xanthen-9-ol and numerous derivatives are being intensively investigated as chemotherapeutic agents, insecticides, pesticides [2,3], photodynamic therapy [4], anti-inflammatory effects [5], and anti viral activity [6]. Several sulfa drugs were tried with 9*H*-xanthen-9-ol and were found to give suitable derivatives [7].

Recently, the reactions of 9*H*-xanthen-9-ol with nucleophilic reagents such as thiol [8], imide [9], indoles [10,11], and thiophene [12] promoted by acids or $BF_3{\cdot}Et_2O$ [11] have been reported. The reaction of xanthene derivatives with indoles and pyrrole catalyzed by CAN through S_N1 reaction of pyrillium with a nucleophilic reagent afforded the corresponding indole- and pyrrole-substituted xanthene derivatives [13]. We have previously reported that $Fe(HSO_4)_3$ as an efficient and recyclable catalyst for the one-pot synthesis of 14-aryl- or alkyl-14*H*-dibenzo[a,j]-xanthene derivatives and 1,3-diaryl-3*H*-benzo[*f*]chromenes [14,15]. This catalyst has emerged as a promising solid acid catalyst for acid catalyzed reactions, such as Friedel–Crafts acylation [16,17], Schmidt reaction [18], Mannich reaction [19], and functional group protections [20,21]. Herein, we report that $Fe(HSO_4)_3$, effectively catalyzes the reactions of 9*H*-xanthen-9-ol **1** with different nucleophilic reagents **2a–j** in ethanol to give 9*H*-xanthen-9-yl derivatives in good to high yields (Scheme 1).

We decided to explore the regioselectivity of heterocyclic systems with different nucleophilic centers (such as **2g**) using a simple marker, 9*H*-xanthen-9-ol **1**. The results of this investigation which lead to the synthesis of *N*-marked product **3g** in the presence of ferric hydrogensulfate catalyst in ethanol reflux conditions. *N*-Alkylation is more favorable than *S*-alkylation of nucleophile or *O*-alkylation of solvent (Scheme 2).

* Corresponding author.
E-mail address: heshghi@ferdowsi.um.ac.ir (H. Eshghi).

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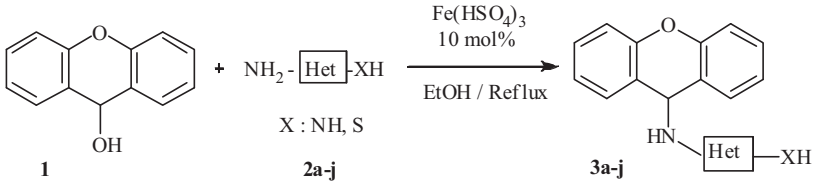
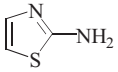
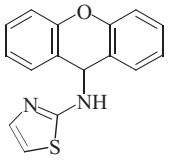
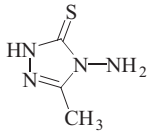
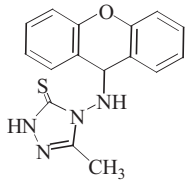
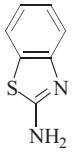
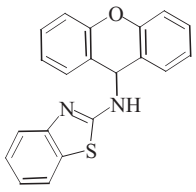
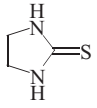
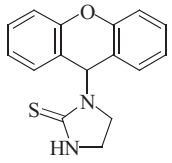
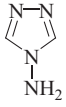
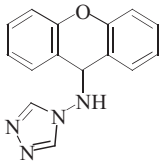
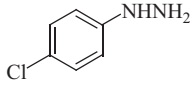
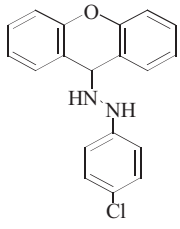
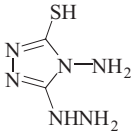
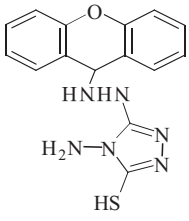
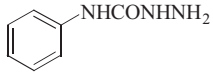
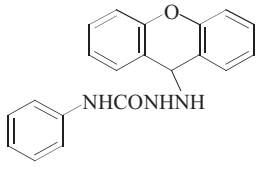
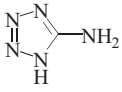
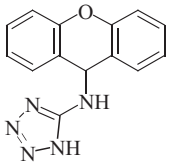
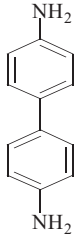
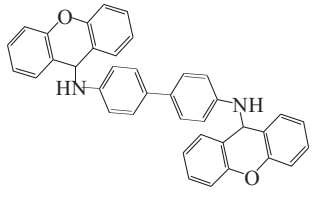
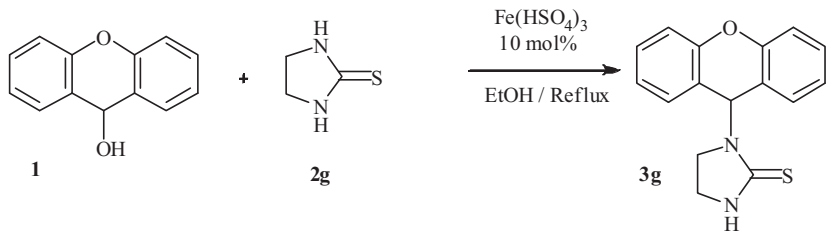


Scheme 1. The reactions of 9*H*-xanthen-9-ol **1** with different nucleophilic reagents **2a–j**.

Table 1
Reaction of nucleophilic reagents **2a–j** with 9*H*-xanthen-9-ol **1** catalyzed by $Fe(HSO_4)_3$ in ethanol.

Entry	Reagent **2**	Product **3**	Time (h)	Yield (%)	Entry	Reagent **2**	Product **3**	Time (h)	Yield (%)
a			1	89	**f**			0.5	92
b			2	85	**g**			2	85
c			0.5	95	**h**			2	95
d			0.5	92	**i**			1	89
e			0.5	96	**j**			0.5	95



Scheme 2. The reactions of 9*H*-xanthen-9-ol **1** with imidazolidine-2-thione **2g**.

The solvent (EtOH) does not compete with nucleophile in this condition. Various nucleophilic reagents **2a–j** employed in this reaction. $Fe(HSO_4)_3$, effectively catalyzes the reactions of 9*H*-xanthen-9-ol **1** with different nucleophilic reagents **2a–j** in ethanol to give 9*H*-xanthen-9-yl derivatives which exclusively *N*-alkylated in good to high yields. The results are listed in Table 1. Primary amines are reacted efficiently over secondary or strickted amines. The structures of compounds **3a–j** were characterized by ^{1}H NMR and IR spectrometry [22]. The ^{1}H NMR spectrum of **3a** showed signals for NH group (δ 4.85 ppm) and methine (δ 5.45, 6.85 and 7.24 ppm), together with multiplet for the aromatic region (6.90–7.36 ppm) protons. IR spectra of compound **3a** show strong absorption bands at 3273 cm^{-1} for the NH group and 3097, 1624, 1515, 1478, 1259, 761, 750 moieties. As a suggested mechanism, $Fe(HSO_4)_3$ promoted the cleavage of the hydroxyl group in compound **1** to give the intermediate pyrylium species it was then attacked by the nucleophilic reagents **2a–j** regioselectively to give the desired product, in competition with nucleophilic solvent without any side products. The pyrylium cation is a conjugated polyaromatic system with one carbon atom replaced by a positively charged oxygen atom. These high nucleophilic selectivities are due to stability of pyrylium cation and new C–N bond formation.

Melting points were determined in open capillary tubes in an Electrothermal IA 9000 melting point apparatus. IR spectra were recorded on an Avatar 370 FT-IR Thermo Nicolet Infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker-100 MHz instrument using tetramethylsilane (TMS) as an internal standard. Elemental analyses were obtained on a Thermo Finnigan Flash EA microanalyzer. Ferric hydrogensulfate was prepared according to previously reported procedure [18].

In conclusion, the present protocol provides a novel, convenient method and highly efficient procedure for the synthesis of novel 9*H*-xanthen-9-yl derivatives of nitrogen contain heterocyclic nucleophiles, through the $Fe(HSO_4)_3$ mediated S_N1 reaction. The simplicity, together with the use of inexpensive, recyclable and environmentally benign nature of catalyst, is other remarkable features of the procedure.

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[22] General procedure: a mixture of 9H-xanthen-9-ol (0.198 g, 1 mmol), nucleophilic reagents 2**a–j** (1 mmol), and $Fe(HSO_4)_3$. (0.035 g, 0.1 mmol) in ethanol (5 mL) was stirred at reflux for appropriate time according to Table 1. The progress of the reaction was monitored by TLC. After the completion, the reaction mixture was filtered and the organic solvent was cooled and concentrated to afford crude product. The crystalline pure product was obtained by further recrystallization from ethanol. Data for new compounds: N-(9H-Xanthen-9-yl)-1, 3-thiazol-2-amine (**3a**): Yellow powder, yield: 0.249 g (89%). mp 188–189 °C, Anal. calcd. for $C_{16}H_{12}N_2OS$ (280.34): C, 68.55; H, 4.31; N, 9.99%. Found: C, 68.53; H, 4.29; N, 9.97%. ^{1}H NMR (100 MHz, $CDCl_3$): δ 4.85 (br, s, 1H, NH), 5.45 (s, 1H, CH), 6.85 (d, 1H, CH), 7.24 (d, 1H, CH), 6.90–7.36 (m, 8H). IR (KBr, cm^{-1}) ν: 3273 (NH), 3097, 1624, 1515, 1478, 1259, 761, 750. N-(9H-Xanthen-9-yl)-1, 3-benzothiazol-2-amine (**3b**): Yellow powder, yield: 0.281 g (85%). mp 230–231 °C, Anal. calcd. for $C_{20}H_{14}N_2OS$ (330.40): C, 72.70; H, 4.27; N, 8.48%. Found: C, 72.68; H, 4.25; N, 8.49%. ^{1}H NMR (100 MHz, $CDCl_3$): δ5.81 (br, s, 1H, NH), 5.62 (s, 1H, CH), 7.15–7.76 (m, 12H). IR (KBr, cm^{-1}) ν: 3162 (NH), 2976, 1594, 1568, 1536, 1481, 1255, 749. N-(9H-Xanthen-9-yl)-4H-1, 2, 4-triazol-4-amine (**3c**): White powder, yield: 0.251 g (95%). mp 236–238 °C, Anal. calcd. for $C_{15}H_{12}N_4O$ (264.28): C, 68.17; H, 4.58; N, 21.20%. Found: C, 68.14; H, 4.60; N, 21.22%. ^{1}H NMR (100 MHz, $CDCl_3$): δ5.40 (d, 1H, NH), 5.55 (d, 1H, CH), 7.08–7.58 (m, 10H). IR (KBr, cm^{-1}) ν: 3217 (NH), 3125, 1481, 1260, 1064, 775, 756, 632. 4-Amino-5-[2-(9H-xanthen-9-yl) hydrazinyl]-4H-1, 2, 4-triazole-3-thiol (**3d**): White powder, yield: 0.300 g (92%). mp 216–218 °C, Anal. calcd. for $C_{15}H_{14}N_6OS$ (326.38): C, 55.20; H, 4.32; N, 25.75%. Found: C, 55.21; H, 4.30; N, 25.70%. ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.15 (br, s, 1H, NH), 4.25 (br, s, 1H, NH), 5.55 (s, 1H, CH), 5.77 (s, 2H, NH_2), 7.05–7.45 (m, 8H), 13.26 (s, 1H, SH). IR (KBr, cm^{-1}) ν: 3346, 3268 (NH), 3212 (NH_2), 1645, 1601, 1481, 1260, 754. N-(9H-Xanthen-9-yl)-1H-tetrazol-5-amine (**3e**): White powder, yield: 0.255 g (96%). mp 235–236 °C, Anal. calcd. for $C_{14}H_{11}N_5O$ (265.27): C, 63.39; H, 4.18; N, 26.40%. Found: C, 63.36; H, 4.15; N, 26.36%. ^{1}H NMR (100 MHz, $CDCl_3$): δ 4.75 (d, 1H, NH), 4.65 (s, 1H, NH), 6.05 (d, 1H, CH), 6.87–7.58 (m, 8H). IR (KBr, cm^{-1}) ν: 3396 (NH), 1576, 1483, 1258, 754. 5-Methyl-4-(9H-xanthen-9-ylamino)-2, 4-dihydro-3H-1,2,4-triazole-3-thione (**3f**): White powder, yield: 0.285 g (92%). mp 201–203 °C, Anal. calcd. for $C_{16}H_{14}N_4OS$ (310.37): C, 61.92; H, 4.55; N, 18.05%. Found: C, 61.90; H, 4.50; N, 18.01%. ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.29 (s, 3H, CH_3), 5.27 (d, 1H, NH), 6.23 (d, 1H, CH), 7.11–7.65 (m, 8H), 10.90 (br, s, 1H, NH). IR (KBr, cm^{-1}) ν: 3252 (NH), 3048, 1578, 1481, 1458, 1258, 756. 2-(9H-Xanthen-9-ylsulfanyl)-4, 5-dihydro-1H-imidazole (**3g**): White powder, yield: 0.240 g (85%). mp 178–179 °C, Anal. calcd. for $C_{16}H_{14}N_2OS$ (282.36): C, 68.06; H, 5.00; N, 9.92%. Found: C, 68.10; H, 5.06; N, 9.90%. ^{1}H NMR (100 MHz, $CDCl_3$): δ 3.15–3.36 (m, 2H, CH_2), 3.42–3.66 (m, 2H, CH_2), 5.81 (br, s, 1H, NH), 7.10 (s, 1H, CH), 7.15–7.68 (m, 8H). IR (KBr, cm^{-1}) ν: 3224 (NH), 2872, 1497, 1479, 1450, 1253, 759. 1-(4-Chlorophenyl)-2-(9H-xanthen-9-yl) hydrazine (**3h**): White powder, yield: 0.307 g (95%). mp 196–197 °C, Anal. calcd. for $C_{19}H_{15}C_lN_2O$ (322.79): C, 70.70; H, 4.68; N, 8.68%. Found: C, 70.67; H, 4.65; N, 8.65%. 1H NMR (100 MHz, $CDCl_3$): δ 5.05–5.21 (m, 2H, NH-NH), 5.30 (d, 1H, CH), 7.04–7.72 (m, 12H). IR (KBr, cm^{-1}) ν: 3256, 3157 (NH), 2966, 1622, 1566, 1263, 756. N-Phenyl-2-(9H-xanthen-9-yl)hydrazinecarboxamide (**3i**): White powder, yield: 0.295 g (89%). mp 234–235 °C, Anal. calcd. for $C_{20}H_{17}N_3O_2$ (331.17): C, 72.49; H, 5.17; N, 12.68%. Found: C, 72.45; H, 5.15; N, 12.65%.1H NMR (100 MHz, DMSO): δ 5.15 (s, 1H, CH), 5.45 (br, s, 1H, NH), 6.75 (br, s, 1H, NH), 8.15 (br, s, 1H, NH), 7.10–7.70 (m, 13H). IR (KBr, cm^{-1}) ν: 3334, 3249, 3240 (NH), 1658, 1537, 1481, 1261, 761. N4, N4′-Di (9H-xanthen-9-yl)-[1,1′-biphenyl]-4, 4'-diamine (**3j**): White powder, yield: 0.517 g (95%). mp 267–268 °C, Anal. calcd. for $C_{38}H_{28}N_2O_2$ (544.64): C, 83.80; H, 5.18; N, 5.14%. Found: C, 83.75; H, 5.15; N, 5.10%. ^{1}H NMR (100 MHz, DMSO): δ 3.65 (br, s, 2H, 2NH), 5.48 (s, 1H, CH), 6.75 (d, 4H, CH ortho), 6.91 (m, 20H). IR (KBr, cm^{-1}) ν: 3468, 3374 (NH), 1625, 1498, 1477, 1445, 1249, 750.