A One-Pot Preparation of 5-Oxo 2,4-Disubstituted 2,5-Dihydro-1*H*-imidazol-2-carboxylates from α-Bromo Esters

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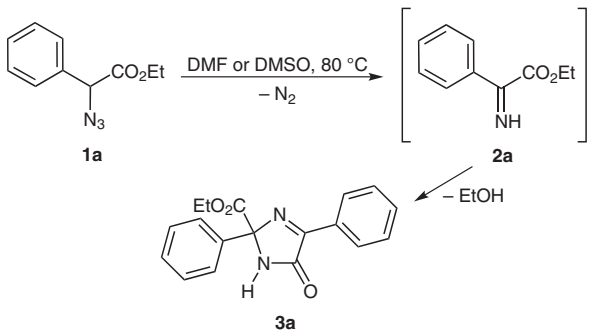
Abstract: Nucleophilic substitution of a bromine atom by the azide group in aryl- and heteroaryl-α-bromoacetates triggers cascade reactions leading to imidazolin-5-ones formation. The α-azidoacetate intermediates undergo a transformation into non-isolable 2-imino esters that dimerize giving the heterocyclic imidazoline system. The process described is strongly promoted by dipolar aprotic solvents (DMF, DMSO) and could be realized under base- and metal-free conditions.

Key words: azides, cyclization, substitution, imidazolin-5-ones, nitrenes

The chemistry of imidazoline derivatives plays an important role in the field of biological and pharmacological sciences. The therapeutic applications of imidazolines and imidazoline-5-ones as anticonvulsant,[1] CNS depressant,[2] sedative and hypnotics,[3] hypotensive[4] and antiparkinsonian agents[5] are well known and have been described in the literature. The newest pharmaceutical investigations of imidazoline-5-one derivatives come from their leishmanicidal activity[6] and strong inhibition of β-secretase[7] (known as BACE1). Some imidazolin-5-ones substituted with aromatic groups indicate the potential for optoelectronic application and they are promising candidates for organic light-emitting diodes (OLEDs), organic solar cells[8] and photosensitizers.[9]

Interest in the practical exploitation of imidazoline-5-one derivatives has resulted in the search for new and simple methods for preparation of this heterocyclic system. Synthesis of the imidazoline-5-one core is usually accomplished in three ways. The first method consists in transformation of 2-oxazolin-5-ones into imidazoline-5-ones in the presence of an amine or Schiff base.[10] The second route is based on intermolecular cyclization of N-substituted α,β-unsaturated amino acid hydrazides.[11] Condensation of α,β-dicarbonyl compounds with guanidine derivatives represents the third procedure for preparation of these heterocyclic products.[7]

During our investigations on thermal stability of organic azides we noted that dipolar, aprotic solvents support transformation of α-azidocarboxylic esters into α-iminocarboxylates. Ethyl α-azido(phenyl)acetate (**1a**) underwent slow and spontaneous decomposition in DMF or DMSO at the room temperature with evolution of nitrogen indicating formation of the nitrene intermediate. Increase of the reaction temperature made the decomposition of α-azido ester faster but the reaction remained controllable at all times. Monitoring of the thermal decomposition of α-azidophenylacetate **1a** at 80 °C by GC gave evidence for conversion into α-imino ester **2a** followed by dimerization to ethyl 5-oxo-2,4-diphenyl-2,5-dihydro-1*H*-imidazol-2-carboxylate (**3a**; Scheme 1). The final heterocyclic product was isolated in very good yield from the reaction mixture and its structure was determined using 2D NMR experiments (COSY, HMBC, HSQC) to assign all NMR signals and confirm the proposed structure.[12] Transformations of α-azido esters into reactive α-iminocarboxylates have been reported previously as decomposition of α-azido ester enolates.[13] The results of our research led us to the conclusion that the conversion of ethyl α-azido(phenyl)acetate (**1a**) into α-imino ester **2a** can be realized not only under basic conditions but also in the absence of any base in dipolar aprotic solvents.



Scheme 1 Transformation of ethyl α-azido(phenyl)acetate (**1a**) into

Efficient formation of the imidazolin-5-ones from α-azido esters was observed only in DMF and DMSO. Analysis of the solvent effects indicated that the highest reaction rate for the conversion of ethyl α-azido(phenyl)acetate (**1a**) into 5-oxo-2,4-diphenyl-2,5-dihydro-1*H*-imidazol-2-carboxylate **3a** at 80 °C occurred in DMSO whereas *n*-butanol gave only traces of the dimerization product. MeCN and toluene did not promote this transformation at all. The spectroscopic data and physical properties determined for **3a** were in accordance with those reported earlier for the same compound prepared by a multistep procedure.[14]

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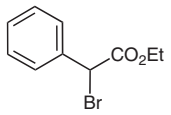
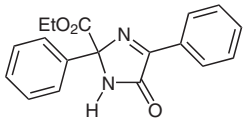
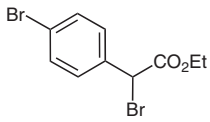
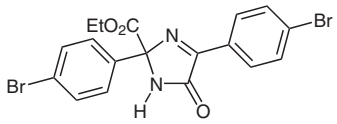
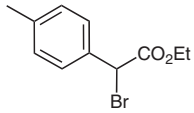
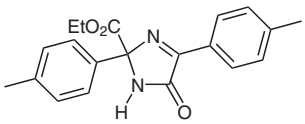
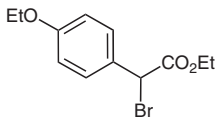
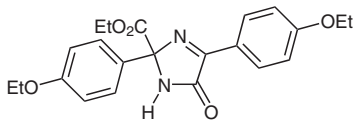
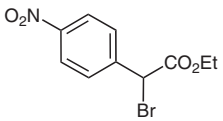
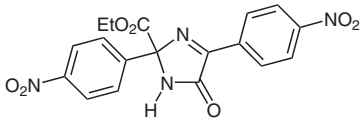
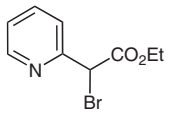
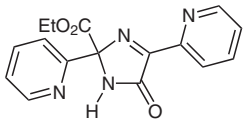
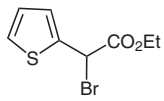
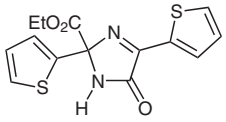
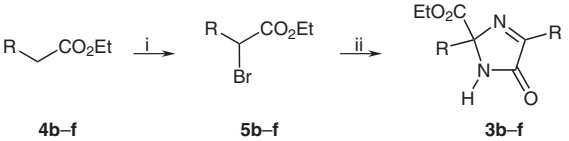
Table 1 Reaction of Ethyl α-Bromoacetates **5a–g** with NaN_3 (1.5 equiv) in DMF at 80 °C Leading to 5-Oxo 2,4-Disubstituted 2,5-Dihydro-1*H*-imidazol-2-carboxylates **3a–g**

Entry	Substrate	Time (h)	Product	Mp (°C)	Isolated yield (%)
1	 **5a**	5	 **3a**	148–149	92
2	 **5b**	30	 **3b**	129–130	85
3	 **5c**	18	 **3c**	130–131	81
4	 **5d**	24	 **3d**	132–133	95
5	 **5e**	30	 **3e**	94–95	34
6	 **5f**	8	 **3f**	73–74	67
7	 **5g**	18	 **3g**	103–104	58

Esters of α-azidocarboxylic acids are not commercially available. The standard procedure for synthesis of α-azido(aryl)acetates consists in the reaction of the appropriate α-bromo esters with sodium azide in DMF, DMSO or MeCN at the room temperature.[15] We noted, that solvent and reaction temperature play the crucial role in the nucleophilic substitution of bromine with azide group in α-bromo(aryl)acetates **5**. Ethyl α-bromo(phenyl)acetate (**5a**) treated with sodium azide in DMF at the room temperature gave ethyl α-azido(phenyl)acetate (**1a**) as the main product. However, the same reaction carried out at 80 °C led to imidazolin-5-one **3a**. GC analysis of the reaction mixture showed nearly complete transformation of α-bromo(phenyl)acetate into imidazolidin-5-one **3a** in four hours and only traces of α-imino(phenyl)acetate **2a** were indicated. We applied the same method for transformations of various α-bromo esters derived from commercially available aryl- and heteroarylacetates, to novel imidazolin-5-one derivatives **3b–f**[16] (Scheme 2). We also found that freshly prepared α-bromo esters **5** could be used without purification,[17] particularly important in relation to unstable α-bromo esters, which undergo decomposition during chromatography or distillation.



4b–f **5b–f** **3b–f**

Scheme 2 Two-step procedure for synthesis of 5-oxo 2,4-disubstituted 2,5-dihydro-1*H*-imidazol-2-carboxylates from commercially available ethyl aryl- and heteroarylacetates. The reactions were carried out without isolation of the intermediate α-azido esters. *Reagents and conditions*: (i) NBS, Luperox®, CCl_4, 74 °C; (ii) NaN_3, DMF, 80 °C.

The experimental observations suggest a 'Type 1' pathway for the decomposition of ethyl α-azido(phenyl)acetate[18] that can be characterized by the initial release of the molecular nitrogen and subsequent isomerization of the nitrene to imine by 1,2-H shift.[19] The mechanism for the conversion of α-imino esters into the imidazolin-5-one heterocyclic system consists of two independent steps, nucleophilic attack and addition of the imine group to the C=N double bond followed by condensation reaction.[20]

Our research shows that formation of the nitrene can be realized in the absence of any base by simple thermal decomposition of α-azidoarylacetates in dipolar aprotic solvents such as DMF or DMSO. We note that simple aliphatic α-azido esters are more stable than α-azidoarylacetates and do not undergo any thermal transformation into nitrene derivatives below 120 °C, so they do not give any aliphatic α-imino esters. We presume that there is a correlation between the thermal stability of α-azido esters and their α-CH acidity. Indeed, diethyl α-bromomalonate, ethyl α-bromonitroacetate and ethyl α-bromocyanoacetate reacted quickly with sodium azide in DMF with accompanying nitrogen evolution even at room temperature. GC of the reaction mixtures showed the absence of α-bromo esters but spectroscopic analysis gave no evidence for formation of imidazolin-5-ones. NMR investigation of crude products indicated the formation of α-imino esters as main products. However, separation of pure α-imino esters was not possible owing to their hydrolytic instability. When we tried to isolate diethyl iminomalonate[21] after reaction of diethyl α-bromomalonate with sodium azide, NMR analysis of the crude extract confirmed the presence of diethyl iminomalonate but its purification using column chromatography failed. However, we noted that this intermediate did not undergo any thermal cyclization and, after one hour of heating to 50 °C, gave a mixture of undefined decomposition products. Intermolecular cyclization of α-imino esters seems to begin with nucleophilic attack of the NH group on a carbon atom at the C=NH double bond and reaction rate depends on the basicity of the nitrogen atom. The presence of electron-withdrawing substituents at α-C reduces the basicity of the imino group and strongly inhibits nucleophilic addition of the NH group onto the C=NH double bond. The low basicity of α-imino esters derived from diethyl α-bromomalonate, ethyl α-bromonitroacetate and ethyl -bromocyanoacetate makes the formation of imidazolin-5-one system impossible.

In summary, our method can be adapted for convenient synthesis of 5-oxo-2,4-diaryl- and 5-oxo-2,4-diheteroaryl-2,5-dihydro-1*H*-imidazol-2-carboxylates from readily available α-bromo(aryl)- and α-bromo(heteroaryl)acetates in a very simple manner. The optimized procedure gives the substituted imidazolin-5-ones in moderate to very good yields.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.25 (s, 1 H, NH), 8.38 (d, 2 H, J_{HH} = 7.8 Hz, CH_{Ar}), 7.62 (m, 2 H, CH_{Ar}), 7.54 (t, 2 H, J_{HH} = 7.8 Hz, CH_{Ar}), 7.44 (t, 2 H, J_{HH} = 7.8 Hz, CH_{Ar}), 7.40 (t, 2 H, J_{HH} = 7.2 Hz, CH_{Ar}), 4.17 (q, 2 H, J_{HH} = 7.2 Hz, CH_3CH_2O), 1.14 (t, 3 H, J_{HH} = 7.2 Hz, CH_3CH_2O). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 167.7, 164.8, 162.9, 137.3, 132.3, 129.6, 128.8, 128.7, 128.4, 128.3, 126.5, 86.5, 62.5, 13.8. All 2D NMR experiments for **3a** were carried out using DMSO-d_6 as a solvent. COSY correlation list: δ [ppm]–δ [ppm](assignment): 1.14–4.17 (CH_3CH_2O), 4.17–1.14 (CH_3CH_2O), 7.40–7.44 (*p*-CH), 7.44–7.40, 7.62 (*m*-CH), 7.54–7.62, 8.38 (*m*-CH), 7.62–7.54 (*p*-CH), 7.62–7.44 (*o*-CH), 8.38–7.54 (*o*-CH). HSQC: correlation list: ^{13}C shift [ppm]–^{1}H shift [ppm](assignment): 13.7–1.14 (CH_3CH_2O), 62.5–4.17 (CH_3CH_2O), 126.5–7.62 (*o*-CH), 128.3–8.38 (*o*-CH), 128.4–7.44 (*m*-CH), 128.7–7.54 (*m*-CH), 128.8–7.40 (*p*-CH), 132.3–7.62 (*p*-CH). HMBC: correlation list: ^{1}H shift [ppm]–^{13}C shifts [ppm] (atom connectivity): 1.14–62.5 (ester group CH_3CH_2O), 4.17–13.7 and 167.7 (ester group CH_3CH_2OCO), 7.40–126.5 (*p*-CH and C-2, phenyl group A), 7.44–126.5, 128.8 and 137.4 (*m*-CH and C-2, C-4, C-1, phenyl group A), 7.54–128.3, 129.6 (*m*-CH and C-2, C-1, phenyl group B), 7.62–86.9, 126.5 and 128.8 (*o*-CH and quaternary C-2 of the imidazolidine ring, C-2, C-4, phenyl group A), 7.62–128.3 (*p*-CH and C-2, phenyl group B), 8.38–128.7, 132.3 and 162.9 (*o*-CH and C-3, C-4 in phenyl group B and C=N in the imidazolidine ring), 11.25–86.9, 162.9 and 164.8 (NH group and quaternary C-2, C=N and C=O in the imidazolidine ring). According to HMBC data,

phenyl substituents A and B were attached to the imidazolidine ring at C-2 and C-4, respectively.

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(16) **General Method for Preparation of Imidazolin-5-ones 3 from α-Bromoacetates**; **Representative One-Pot Synthesis of Ethyl 2,4-Bis(4-ethoxyphenyl)-5-oxo-2,5-dihydro-1*H*-imidazole-2-carboxylate (3d)**: Ethyl α-bromo-2-(4-ethoxyphenylacetate) (**4d**; 1.254 g, 4.4 mmol) and sodium azide (0.428 g, 6.6 mmol, 1.5 equiv) were added to DMF (20 mL). The suspension was stirred and heated for 24 h at 80 °C. After cooling, the reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with H_2O (2 × 50 mL) and dried over anhyd Na_2SO_4. The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using silica gel (230–400 mesh; $CHCl_3$–MeOH, 30:1) to give **3d** as colorless crystals (TLC silica gel; Fluka 60778; $CHCl_3$–MeOH, 30:1; R_f 0.55); mp 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, 2 H, J_{HH} = 9.1 Hz, CH_{Ar}), 8.40 (br s, 1 H, NH), 7.50 (d, 2 H, J_{HH} = 9.0 Hz, CH_{Ar}), 6.95 (d, 2 H, J_{HH} = 9.1 Hz, CH_{Ar}), 6.89 (d, 2 H, J_{HH} = 9.0 Hz, CH_{Ar}), 4.25 (2 × dq, 2 H, J_{HH} = 7.11, 7.14, 10.7 Hz, OCH_2), 4.10 (q, 2 H, J_{HH} = 7.0 Hz, OCH_2), 4.02 (q, 2 H, J_{HH} = 7.0 Hz, OCH_2), 1.44 (t, 3 H, J_{HH} = 7.0 Hz, Me), 1.40 (t, 3 H, J_{HH} = 7.0 Hz, Me), 1.26 (t, 3 H, J_{HH} = 7.1 Hz, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (COOEt), 165.7 (CONH), 162.3 (C=N), 161.6 (C4), 159.5 (C4), 130.8 (C3), 129.0 (C1), 127.4 (C3), 122.3 (C1), 114.6 (C2), 114.4 (C2), 86.0 (C2-imidazolidine), 63.6 (OCH_2), 63.5 (OCH_2), 62.9 (OCH_2), 14.7 (Me), 14.7 (Me), 14.0 (Me). IR (neat): 3168, 3071, 2979, 2936, 1742, 1705, 1595, 1571, 1512, 1237, 1172 cm^{-1}. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 66.45; H, 6.01; N, 7.10.

(17) **Standard Procedure for Synthesis of α-Bromoacetates from Commercial Ethyl Aryl- and Heteroarylacetates; Representative Preparation of Ethyl Bromo(4-ethoxyphenyl) Acetate (4d)**: Ethyl 4-ethoxyphenylacetate (1.695 g, 8.14 mmol) was treated with NBS (1.449 g, 1 equiv) and Luperox® A70S (0.176 g, 0.50 mmol) in CCl_4 (30 mL). The reaction mixture was stirred and heated for 30 h at 74 °C. After cooling the solution was filtered through a Celite pad and the solvent was evaporated. The crude product, ethyl bromo(4-ethoxyphenyl) acetate (**4d**), was pure enough to be used for the next step.

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(21) Partial NMR data for diethyl iminomalonate were determined from the crude reaction mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.76 (br s, 1 H, NH), 4.29 (q, 2 H, J_{HH} = 7.1 Hz, OCH_2), 1.30 (t, 3 H, J_{HH} = 7.1 Hz, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0 (COOEt), 152.3 (C=NH), 61.6 (OCH_2), 14.3 (Me).