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Domino transformation of isoxazoles to 2,4-dicarbonylpyrroles under Fe/Ni relay catalysis

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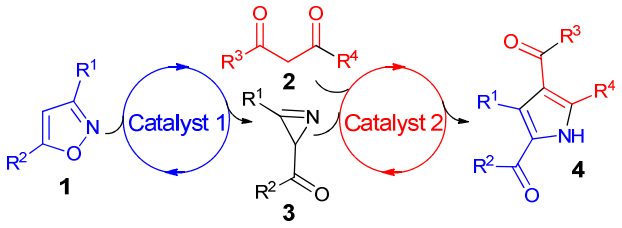
The domino reaction of 5-alkoxy- or 5-aminoizoxazoles, under metal relay catalysis, with symmetric 1,3-diketones gives 4-acylpyrrole-2-carboxylic acid derivatives in high yield. Esters and amides of acylacetic acids react regioselectively, giving derivatives of pyrrole-2,4-dicarboxylic acid as the main products.

Pyrroles, indoles and other fused pyrrole derivatives are viewed by medicinal chemists as privileged structures.[1] These heterocyclic fragments are widely present in natural compounds, pharmaceuticals and material molecules.[2] Not surprisingly, the development of methods for the synthesis of pyrrole derivatives is still a very active area of research[3], although classical methods for the synthesis of such structures are well known. Straightforward and selective routes to synthesize pyrrole derivatives using cheap and available starting materials are therefore highly attractive. Multicatalysis is currently one of the most promising approaches for the construction of molecular frameworks in a resource-efficient and sustainable manner.[4] Application of this approach for the synthesis of compounds with a pyrrole fragment has been utilized, as yet, only for the synthesis of certain indoles. Thus, Ackermann developed a three-component synthesis of substituted indoles by the use of a multicatalytic system consisting of an N-heterocyclic carbene palladium complex and CuI.[5] Peng, Wu and coworkers reported the approach to indole derivatives through a multicatalytic one-pot Beckmann rearrangement-intramolecular cyclization-halogenation reaction of 1-(2-alkynylphenyl)ketoxime.[6] No syntheses of pyrroles under multicatalysis have been published to the best of our knowledge, and only some pyrrolines were prepared using the multicatalytic concept.[7] Maruoka and coworkers found an enantioselective synthesis of the pyrrolidine core structure starting from glycine esters in combination with several different organocatalytic reactions.[7a] Cernak and Lambert developed a synthesis of pyrrolidinyl ketones by incorporation of a catalytic aminochlorocarbonylation into double and triple catalytic processes involving Friedel-Crafts acylation.[7b] Wang and coworkers discovered an aza-Michael/carbocyclization reaction of α,β-unsaturated aldehydes and *N*-tosyl propargylamines under organo/metal cooperative catalysis, leading to chiral pyrrolines.[7c]

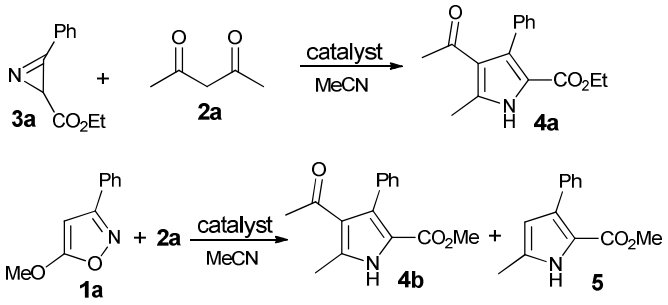
In this communication, we wish to report the first example of a preparation of pyrroles by the domino reaction of isoxazoles and 1,3-dicarbonyl compounds under metal relay catalysis. Auricchio and coworkers[8] found that 5-10 mol% of $FeCl_2 \cdot 4H_2O$ effectively catalyzes the transformation of 3-aryl-5-methoxy/alkylamino-isoxazoles to derivatives of 3-aryl-2*H*-azirine-2-carboxylic acid at room temperature. In turn, 2*H*-azirines react with 1,3-dicarbonyl compounds to give substituted pyrroles.[9,10] These reactions usually need the transformation of the 1,3-dicarbonyl compound into the corresponding metal-enolate[10a] or catalysis by transition metals, $Ni(acac)_2$,[10b] $Cu(acac)_2$ [10c-e] or $VO(OSiPh_3)_3$.[10f] We envisioned that the application of the multicatalysis concept would permit the transformation 1→3+2→4 as a domino reaction (Scheme 1), without isolation of 2*H*-azirines, which are often unstable under isolation and storing.[9]



Scheme 1 Relay catalysis scheme for the synthesis of pyrroles **4** from isoxazoles **1**.

Test experiments were performed with 5-methoxy-3-phenylisoxazole **1a**, acetylacetone **2a**, and ethyl 3-phenyl-2*H*-azirine-2-carboxylate **3a** as starting materials (Table 1). At the beginning we attempted to obtain pyrrole **4a** from azirine **3a** and acetylacetone **2a** under conditions used by Auricchio and coworkers[8] for the transformation of 5-alkoxyisoxazoles **1** into azirines **3** (Table 1, entry 1), but the starting materials were left unchanged even after a longer reaction time.

Table 1 Optimization of the reaction conditions for the transformation of isoxazoles to pyrrole

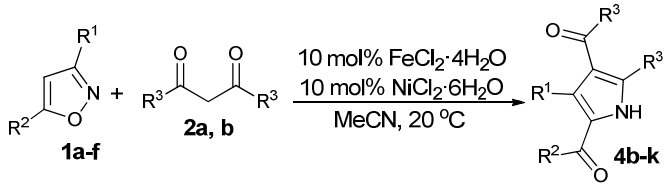


Entry	Reactants	Catalyst	Reaction conditions	Yield of products, %
1	**3a**+**2a**	10 mol% $FeCl_2·4H_2O$	20 °C, 10 d	-
2	**3a**+**2a**	10 mol% $Cu(OAc)_2·H_2O$	20 °C, 10 d	-
3	**3a**+**2a**	10 mol% $NiCl_2·6H_2O$	20 °C, 24 h	**4a**, 77%
4	**1a**+**2a**	10 mol% $NiCl_2·6H_2O$	20 °C, 2 weeks	-
5	**1a**+**2a**	1) 10 mol% $FeCl_2·4H_2O$; 2) 10 mol% $NiCl_2·6H_2O$	1) 20 °C, 2 h; 2) 20 °C, 24 h	**4b**, 82%
6	**1a**+**2a**	10 mol% $FeCl_2·4H_2O$ + 10 mol% $NiCl_2·6H_2O$	20 °C, 24 h	**4b**, 82%
7	**1a**+**2a**	20 mol% $FeCl_2·4H_2O$	65 °C, 20 h	**4b**, 56%; **5**, 17%

The use of $Cu(OAc)_2·H_2O$ was also unsuccessful (Table 1, entry 2), whereas 77% of pyrrole **4a** was obtained with $NiCl_2·6H_2O$ as catalyst (Table 1, entry 3). Attempts to prepare pyrrole **4b** by reaction of isoxazole **1a** and acetylacetone **2a** with $NiCl_2·6H_2O$ as catalyst were unsuccessful (Table 1, entry 4). Therefore, multicatalysis with $FeCl_2$ and $NiCl_2$ in a sequential (Table 1, entry 5) and simultaneous (Table 1, entry 6) manner was tried and gave pyrrole **4b** in good yield. It was also found that the use of 5 and 1 mol% $NiCl_2·4H_2O$ instead of 10% increases the reaction time by 1.5 and 5 times, respectively. The use of $FeCl_2$ as the lone catalyst also gave pyrrole **4b**, but only under heating and in lower yield (Table 1, entry 7). Byproduct, pyrrole **5**, also arose from decarbonylation under these conditions. Therefore, the reaction conditions listed in entry 6 of Table 1 were used further for the preparation of a series of pyrrole-2-carboxylic acid derivatives, starting from isoxazoles **1a-h** and diones **2a**, **b**. This very simple procedure afforded compounds **4b-e, g-k** in good yields, except for compound **4f** with a 4-$Me_2NC_6H_4$ substituent (Table 2). The lowering of the yield in this case was probably caused by the instability of the transient azirine and pyrrole **4f** under these reaction conditions.

The structures of compounds **4b-k** were verified by ^1H and ^{13}C NMR, IR spectroscopy, and mass-spectrometry. The spectral and physical data for known compounds **4b, g** corresponds to published data.[11, 12]

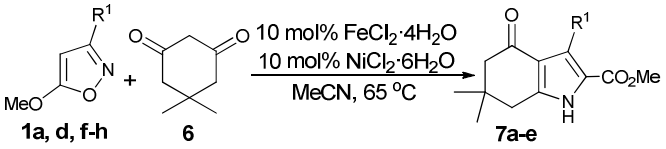
Table 2 Synthesis of pyrroles **4b-k**



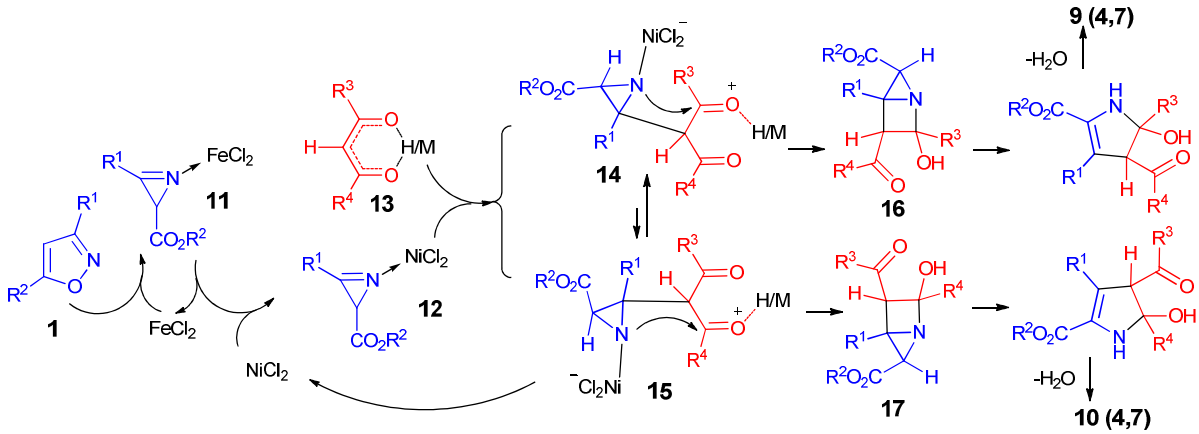
Entry	R^1	R^2	R^3	**1**	**2**	Time, d	Yield of **4**, %
1	Ph	MeO	Me	**a**	**a**	1	**b**, 82
2	Ph	*t*BuO	Me	**b**	**a**	2	**c**, 81
3	Ph	$(CH_2)_4N$	Me	**c**	**a**	1	**d**, 71
4	4-ClC_6H_4	MeO	Me	**d**	**a**	1	**e**, 92
5	4-$Me_2NC_6H_4$	MeO	Me	**e**	**a**	1	**f**, 23
6	Ph	MeO	Ph	**a**	**b**	2	**g**, 90
7	4-BrC_6H_4	MeO	Ph	**f**	**b**	1	**h**, 64
8	4-$MeOC_6H_4$	MeO	Ph	**g**	**b**	2	**i**, 72
9	Me	MeO	Me	**h**	**a**	2	**k**, 87

Because of the important bioactivity of compounds with a tetrahydroindolone skeleton[13] the multicatalysis approach for the domino preparation of these indole derivatives was investigated. Reaction of dimedone **6** with isoxazoles **1** under the conditions used for the preparation of pyrroles **4b-k** was too slow at room temperature. It was found that heating at 65 °C makes the rates of the reactions acceptable and tetrahydroindolones **7a-d** were obtained in good yields from 3-arylisoxazoles **1** (Table 3). 3-Methylisoxazole **1h** gave tetrahydroindolones **7e** in low yield, probably due to the instability both of the isoxazole and the corresponding transient azirine at 65 °C.

Table 3 Synthesis of tetrahydroindolones **7a-e**



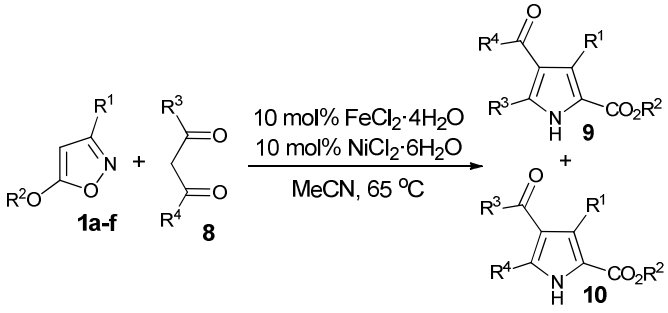
Entry	R^1	**1**	Time, h	Yield of **7**, %
1	Ph	**a**	8	**a**, 86
2	4-ClC_6H_4	**d**	10	**b**, 70
3	4-BrC_6H_4	**f**	8	**c**, 70
4	4-$MeOC_6H_4$	**g**	36	**d**, 76
5	Me	**h**	12	**e**, 18



Scheme 2 Plausible mechanism for the relay metal catalyzed reaction of isoxazoles and 1,3-dicarbonyl compounds

The reactions of isoxazoles **1** with 3-oxopropanoates **8** are also slower than with acyclic diketones **2** and therefore were carried out with heating (Table 4).

Table 4 Synthesis of derivatives of pyrrole-2,4-dicarboxylic acid **9a-e**



Entry	R^1	R^2	R^3	R^4	**1**	**8**	Time, h	Yield of **9**, %	Yield of **10**, %
1	Ph	Me	Ph	EtO	**a**	**a**	72[a]	**a**, 52	**a**, 12
2	4-ClC_6H_4	Me	Ph	EtO	**d**	**a**	10	**b**, 47	**b**, 17
3	4-$MeOC_6H_4$	Me	Ph	EtO	**g**	**a**	10	**c**, 33	**c**, 11
4	Ph	*t*Bu	Me	EtO	**b**	**b**	9	**d**, 34	-
5	Ph	Me	Me	EtO	**a**	**b**	9	**e**, 58	-
6	4-ClC_6H_4	Me	Me	EtO	**d**	**b**	8	**f**, 40	**d**, 4
7	4-BrC_6H_4	Me	Me	EtO	**f**	**b**	8	**g**, 41	**e**, 11
8	4-$Me_2NC_6H_4$	Me	Me	EtO	**e**	**b**	8	**h**, 36	-
9	4-$MeOC_6H_4$	Me	Me	EtO	**g**	**b**	8	**i**, 51	-
10	Ph	Me	Me	PhHN	**a**	**c**	6	**k**, 50	-
11	4-BrC_6H_4	Me	Me	PhHN	**f**	**c**	6	**l**, 65	-

[a] Room temperature.

In this case the reaction can proceed via the two different carbonyl groups of **8** to give two isomeric pyrroles **9** and **10**. Derivatives of pyrrole-2,4-dicarboxylic acid **9** were the main products (yields of 33-65%). Minor products, 5-ethoxypyrroles **10a-c**, were formed in all the reactions performed with ethyl 3-oxo-3-phenylpropanoate **8a**, and 5-ethoxypyrroles **10d, e** were formed in reactions of 4-halophenyl-substituted isoxazoles **1d**, **f** with ethyl acetoacetate **8b**. Replacing the ester group by the less electrophilic amide group (**8b** → **8c**) makes the reaction regioselective, giving only derivatives **9** even with isoxazole **1f**. The plausible mechanism for the metal-catalyzed reaction of isoxazoles with 1,3-dicarbonyl compounds is presented on scheme 2. We assume that isoxazole **1** reacts with $FeCl_2$, giving the unstable azirinium complex **11**, which undergoes transmetalation with formation of Ni-complex **12**. The latter reacts with the enol-form (or metal-enolate) **13** of compounds **2**, **6** or **8**, giving intermediate **14/15** (**14**=**15** in the case of compounds **2**, **6** with $R^3 = R^4$). The attack of the aziridine nitrogen on the quasi protonated/metalated $C{=}O^+H/M$ group of **14/15** leads to intermediate **16/17**. Intermediates **16/17** give pyrroles **4**, **7**, **9/10** via aziridine ring opening and elimination of H_2O. The regioselectivity of the reaction in the case of compounds **8** in favour of pyrrole **9** is obviously caused by a shift of the equilibrium **14**⇆**15** to the **14** side (R^4 = OEt, NHPh).

Conclusions

A simple procedure for the preparation of derivatives of 4-acylpyrrole-2-carboxylic acid, 4,5,6,7-tetrahydro-4-oxo-1*H*-indole-2-carboxylic acid, and pyrrole-2,4-dicarboxylic acid by domino reaction of 5-alkoxy- or 5-aminoizoxazoles with 1,3-dicarbonyl compounds under Fe(II)/Ni(II) relay catalysis was developed. The approach is especially effective using symmetric 1,3-diketones as starting materials. Esters and amides of acylacetic acids react regioselectively giving derivatives of pyrrole-2,4-dicarboxylic acid as the main products, but in lower yields.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and characterization data. See DOI: 10.1039/c000000x/

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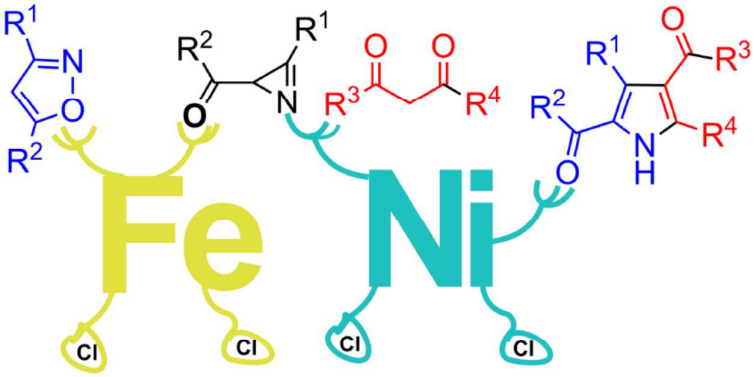
Graphical Abstract



R^1 = Ar, Me; R^2 = OAlk, NR_2; R^3 = R^4 = Ph, Me;
$R^3 + R^4 = CH_2CMe_2CH_2$; R^3 = OEt, NHPh; R^4 = Ph, Me