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New application of heterocyclic diazonium salts. Synthesis of pyrazolo[3,4-*d*][1,2,3]triazin-4-ones and imidazo[4,5-*d*][1,2,3]triazin-4-ones

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ABSTRACT

The pyrazolo[3,4-*d*][1,2,3]triazin-4-ones **3** and imidazo[4,5-*d*][1,2,3]triazin-4-ones **4** are analogs structurally related to purines that have showed a wide and significant variety of biological activity. These compounds were synthesized by one-pot diazotization of 5-amino-1*H*-pyrazole-4-carbonitriles **1** and 5-amino-1*H*-imidazole-4-carbonitriles **2**, respectively.

1. Introduction

Heterocyclic compounds structurally related to purine rings as pyrazolo[3,4-*d*][1,2,3]triazin-4-ones and imidazo[4,5-*d*][1,2,3]triazin-4-ones have shown important anticonvulsant activity,[1] they have also been reported as antifungal, antiviral, and anticancer agents.[2–6] Numerous synthetic compounds containing the 1,2,3 triazine ring are also used as pharmaceuticals, herbicides, pesticides, dyes, etc.[7–9] Consequently, there is a continuous widespread interest in the design and synthesis of novel purine analogs and heterocyclic compounds containing the triazine moiety because of the potential biological activities associated with these systems.

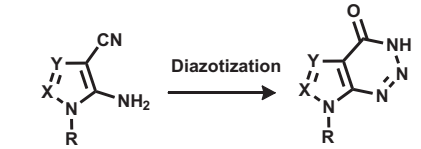
In general, the synthesis of purine-type compounds from simple or non commercial molecules involves several reactions, leading to different azolotriazines in moderate to low yields.[6,10] Diazonium ion condensation with an adjacent nucleophilic function to form a five- or six-membered ring has proved a valuable tool for the synthesis of various nitrogen fused-heterocycles. Thus, we have prepared new derivatives of pyrazolo[3,4-*d*][1,2,3]triazin-4-ones in a convenient one-pot diazotization of 5-amino-1*H*-pyrazole-4-carbonitriles.[11]

In our attempt to obtain heterocyclic compounds of biological interest and following our work on the synthesis of azolotriazines, we prepared different 7-aryl-4*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4-ones **3b–d** by diazotization of aminopyrazoles **1b–d** and 6-benzyl-4*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4-one **12** by diazotization of **5**. In order to explore the scope of this synthetic strategy, the utilization of 5-amino-1*H*-imidazole-4-carbonitriles precursors **2a–c** for the synthesis of new imidazo[4,5-*d*][1,2,3]triazin-4-ones **4a–c** was studied (Fig. 1). As a part of the analysis of the whole synthetic sequence, we also discuss the effect of the reaction conditions in the preparation of aminopyrazole using hydrazine hydrochloride salts as starting material.

2. Results and discussion

2.1. Synthesis of 5-amino-1*H*-pyrazole-4-carbonitriles

Initially, our work was conducted with the synthesis of 5-amino-1*H*-pyrazole-4-carbonitriles **1a–d** using ethoxymethylene-mal-



1a X= N, Y= C, R= Ph
1b X= N, Y= C, R= *p*-OCH_3Ph
1c X= N, Y= C, R= *o*-FPh
1d X= N, Y= C, R= Bn
2a X= C, Y= N, R=*p*-CH_3Ph
2b X= C, Y= N, R= *p*-OCH_3Ph
2c X= C, Y= N, R= *p*-ClPh

3a-d X= N, Y= C
4a-c X= C, Y= N

Figure 1. Diazotization of aminoazoles **1**and **2** to give azolotriazines **3** and **4**.

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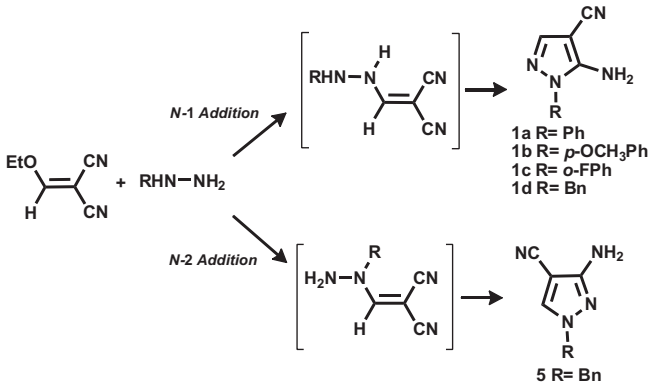
ononitrile and monosubstituted hydrazines as in a previously reported method, which is the general procedure that make reference to the synthesis of these aminopyrazoles.[12] The preparation of pyrazole **1a** was optimized in our previous work.[11] Synthesis of **1b** and **1c** was carried out using hydrazine monohydrochloride while in the case of **1d** benzylhydrazine dihydrochloride was used as source of hydrazine. In these cases a previous step of neutralization with sodium methoxide solution (25% w/v) was needed. Thus, using one equivalent of a solution of NaOMe as a base, the compound **1c** was obtained in good yields; however, in the synthesis of **1b** a high decomposition reaction mixture was obtained without the possibility of isolating the desired product. In order to improve the yields and decrease the decomposition observed in the methoxide neutralization step, triethylamine (TEA) was used as a base. Thus, using one equivalent of TEA, both pyrazoles (**1b** and **1c**) were obtained in high yields as compared to those obtained by the methodology described above (Scheme 1 and Table 1).

Particularly, when the synthesis of compound **1d** was carried out using two equivalents of solution of NaOMe as a base to neutralize the benzylhydrazine dihydrochloride, a mixture of two aminopyrazoles was obtained: the expected and main product **1d**, and the isomer and secondary product **5** (Scheme 1). The formation of **5** is believed to take place by the initial reaction of the *N*-2 nucleophilic center of the benzylhydrazine following by cyclization. It is known that under neutral or acidic conditions and if the nucleophilicity of the two nitrogen atoms of the hydrazine is quite different the most abundant isomer corresponds to the 1,2-addition at the terminal NH_2 group of the hydrazine to the most reactive center in the 1,3-difunctional compound.[13] However, when *N*-1 and *N*-2 of the hydrazine present similar nucleophilicity a mixture of regioisomers is obtained. Said situation is observed in our reactions using benzylhydrazine. As can be seen from the results outlined in Table 1, the formation of **1d** was favoured over



Scheme 1. Synthesis of aminopyrazole-carbonitriles.

Table 1
Effects of reaction conditions on the synthesis of aminopyrazoles

Conditions base, equivalents	Time (h)	Yield (%) 1b	1c	1d	5
NaOMe, 1	2	ND[a]	76[b]	47[b]	—
				100[c]	—
TEA, 1	4	69[b]	91[b]	49[b]	—
				100[c]	—
NaOMe, 2	2	—		34[b]	13[b]
				72[c]	28[c]
TEA, 2	4	—		41[b]	9[b]
				82[c]	18[c]

[a] Not done due to high decomposition.
[b] Isolated yields.
[c] Relative yields of isomers determined by ^{1}H NMR.

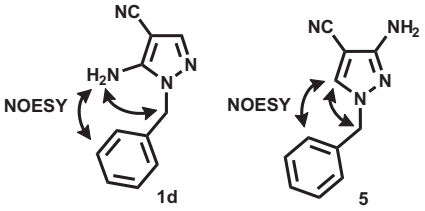


Figure 2. NOE correlation 2D observed for isomers **1d** and **5**.

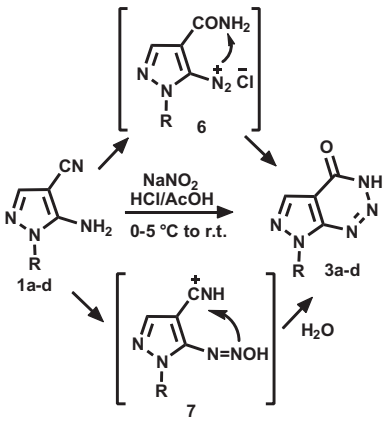
isomer **5** under all evaluated conditions, while **5** was obtained when two equivalents of base were used. The amount of **5** was slightly increased when NaOMe was used for the neutralization step. A similar behavior was observed in the synthesis of benzylpyrazoloquinolinones derivatives.[14] On the other hand, it should be mentioned that isomer **1d** was exclusively obtained when pure and distilled benzylhydrazine was used in this reaction.[15]

The structural assignment of **1d** and **5** was made on the basis of their 1D and 2D NMR spectra. The ^{1}H NMR experiment of **1d** showed the typical signal for the vinylic proton at *C*-3 at 7.58 ppm, while in the case of proton at *C*-5 in **5** appeared as a low field signal at 8.25 ppm. ^{13}C NMR analysis showed similar signals for both isomers and were not useful to distinguish between them. Conversely, NOESY experiments were crucial since in **1d** the correlation of NH_2 protons with methylene and aryl protons were observed, while in the case of **5**, the correlation of the *C*-5 proton with methylene and aryl protons was achieved (Fig. 2).

2.2. Synthesis of pyrazolo[3,4-*d*][1,2,3]triazin-4-ones

Compounds **3a–d** were synthesized by diazotization reaction involving 5-amino-1*H*-pyrazole-4-carbonitriles **1a–d** and aqueous $NaNO_2$ in a mixture of HCl/AcOH (3:1).[16] In all cases, the new azolotriazinones **3b–d** were obtained in good to very good yields depending on the substituent at *N*-1 (Scheme 2 and Table 2). The reaction is assumed to take place by the intermediacy of a diazocarboxamide **6** and/or a diazoic acid **7** which could give an intramolecular triazine ring closure.[11] In the first case the amide group in the species **6** could be obtained by 'in situ' hydrolysis of the cyano group. In the second case the diazohydroxide form **7** is a tautomer of the initial nitrosoamine formed under diazotization conditions where cyano group could be also protonated.

As it was found in the literature, the cyclization of pyrazolediazonium ion highly depends on the electrophilicity of the diazo group and on the stability of the diazonium salt under the reaction conditions described.[17] Thus, this stability is affected by



Scheme 2. Synthesis of pyrazolo[3,4-*d*][1,2,3]triazin-4-ones.

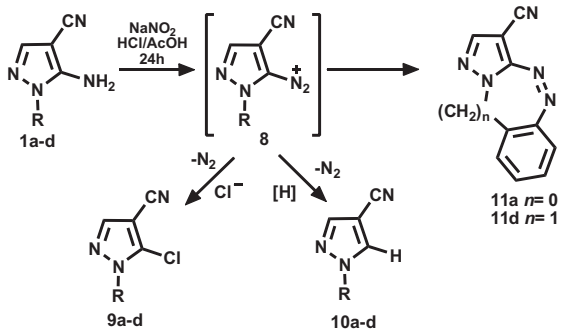
Table 2
Yields of formation of pyrazolotriazines **3**

Compd	R	Yield[a] (%)
3a	Ph	77[b]
3b	*p*-OCH_3Ph	88
3c	*o*-FPh	64
3d	Bn	50
3e	*tert*-Bu	47[b]
3f	*p*-FPh	70[b]

[a] Isolated yields.
[b] Ref. 11.

the nature of different substituents attached to the *N*-1 of the pyrazole ring. To evidence this effect, the results obtained for all pyrazolotriazinones (synthesized here and in a previous work) are shown in Table 2. It can be seen that the presence of fluorophenyl groups as well as alkyl groups in the starting pyrazole resulted in lower yields in the synthesis of **3c–f** than in the synthesis of **3a**. On the contrary, a *p*-methoxyphenyl group in *N*-1 position favored the reaction and **3b** was obtained with the highest yield. Therefore, the presence of an electron releasing group in *N*-1 of the pyrazole ring may promote the stabilization of the diazo-intermediates (**6** and/or **7**) and their cyclization reaction, while a withdrawing or an alkyl substituent did not facilitate such kind of reaction and the yields obtained were lower.

Apart from pyrazolotriazinones, side products (1–10% yields) were obtained in the reaction mixture: 5-chloropyrazole-4-carbonitriles **9**, pyrazole-4-carbonitriles **10** and fused-pyrazoles **11**. Formation of these products could be explained by reactions of the diazonium ion **8** (Scheme 3). Compounds **9** are the expected products when the diazotization solution is stirred in the presence of concentrated HCl or in diluted acid for longer periods; under these conditions **8** can be substituted by chlorine.[17] It is well known that this substitution takes place by different mechanisms and that this is strongly dependant on the reaction conditions.[18] The formation of pyrazoles **10** is thought to proceed by a hydro-dediazoniation process. The mechanism of this process is unknown, but it may be that diazonium intermediate is trapped by the solvent.[19] On the other hand; the formation of bicyclic pyrazoles **11** from phenyl and benzyl derivatives **1a** and **1d** could be explained in terms of an intramolecular coupling of the diazonium intermediates **8** with the aromatic rings via an electrophilic aromatic substitution (Scheme 3). According to the results here obtained, it was found that *N*-1 substitution affected this reaction. Thus, the presence of a fluorophenyl group avoided the cyclization of diazonium ion **8** onto the aryl ring. Clearly, the electrophilic substitution was not promoted by the inductive withdrawing effect of fluorine. Contrary to what was expected, in the synthesis of **3b**, the product formed by electrophilic aromatic substitution was not even obtained with an electron releasing group, as a methoxy group, that should have



Scheme 3. Formation of side products **9**, **10** and **11**.

activated the aromatic ring towards this type of reaction. Thus, the formation of azines **11** was promoted in two cases: (a) when there was not substitution at the phenyl ring, it means in aminopyrazole **1a**; and (b) when benzylpyrazole **1d** was used.

In order to test the reactivity of isomers **1d** and **5** towards the diazotation reaction, a mixture of these pyrazoles was subjected to $NaNO_2$ in acid media (Scheme 4). The corresponding pyrazolotriazines **3d** and **12** could be obtained and isolated from the reaction crude. This experiment clearly showed that the diazo-intermediate arised from **5** also proceed to the triazine ring closure as well as from 5-aminopyrazoles **1**. The structure of **12** was confirmed by its NMR spectra. Particularly, in the homonuclear ROESY experiment, the correlation of the methylene protons could be observed when the *C*-5 proton irradiated.

2.3. Synthesis of 5-amino-1*H*-imidazole-4-carbonitriles

Afterward, 5-amino-1*H*-imidazole-4-carbonitriles **2a–c** were obtained by a sequence of reactions described in the literature.[20] Initially, diaminomaleonitrile (**13**) reacted with triethyl orthoformate in refluxing dry dioxane to give imidate **14** in moderate yields (45%). Then formamidines **15** were obtained by nucleophilic substitution reaction of imidate **14** with different anilines in ethanol at room temperature. In the last step, the cyclization to give 5-amino-1*H*-imidazole-4-carbonitriles **2** was achieved by treatment of formamidines **15** in aqueous potassium hydroxide 1 M. All aminoimidazoles are not described in the literature and were synthesized in good to excellent yields (Scheme 5).

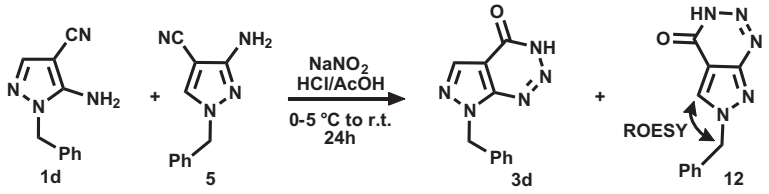
2.4. Synthesis of imidazo[4,5-*d*][1,2,3]triazin-4-ones

As outlined in Scheme 6 and Table 3, imidazotriazinones **4a–c** were subsequently prepared by diazotization of 5-amino-1*H*-imidazole-4-carbonitriles **2a–c** with $NaNO_2$ in a mixture of aqueous HCl/AcOH (3:1) as described above for the synthesis of pyrazolotriazinones **3a–d**. The complete conversion of starting imidazoles was obtained in all cases and yields of isolated products (41–90%) were strongly dependant on the success of the workup. The formation of side products was not observed in these reactions, contrary to what was found in the reactions of **1a–d** to obtain **3a–d** were competitive reactions as displacement of nitrogen elimination and substitutions did not take place.

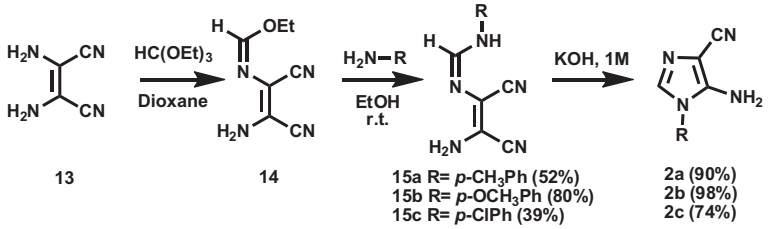
Regarding the stability of diazo intermediates involved in the diazotization of structural isomers pyrazole and imidazole, the diazonium group would be better stabilized by the imidazole ring than the pyrazole ring. In recent computational studies of the bonding and the stability of the intermediates generated from **1b** and **2b**, the electron-density distribution analyzes reveal a mayor stabilization of diazonium ion by the imidazole nucleus. These findings could explain the absence of the dediazoniation process and the favored cyclization of imidazole-diazo intermediates to triazinone rings. In this sense, it was found that the diazo compound obtained by diazotization of 5-aminoimidazole-4-carboxamide readily cyclized to 2-azahypoxanthine, and this cyclization was more rapid than photofluorodediazonization, avoiding the synthesis of 5-fluoroimidazole-4-carboxamide.[21]

3. Conclusions

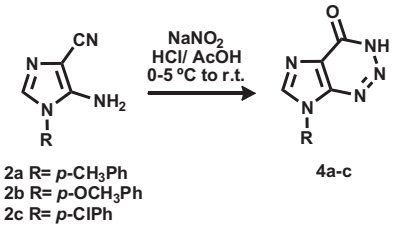
New pyrazolotriazines **3b–d** and imidazotriazines **4a–c** were obtained from aminopyrazoles **1b–d** and aminoimidazoles **2a–c** in a 'one-step' process. In both cases, different azolotriazines could be synthesized from good to very good yields in a simple and efficient methodology.



Scheme 4. Diazotization of a mixture of **3d** and **5**.



Scheme 5. Synthesis of 5-amino-1*H*-imidazole-4-carbonitriles.



Scheme 6. Synthesis of imidazo[4,5-*d*][1,2,3]triazin-4-ones.

Table 3
Yields of formation of imidazotriazinones **4**

Compd	R	Yield[a] (%)
4a	*p*-CH_3Ph	56
4b	*p*-OCH_3Ph	90
4c	*p*-ClPh	41

[a] Isolated yields.

In addition, 5-amino-1-benzyl-1*H*-pyrazole-4-carbonitrile **1d** was selectively obtained when benzylhydrazine dihydrochloride was neutralized with only one equivalent of base disregarding the nature of the base used. Alternatively, the regioisomer **5** was obtained as side product when two equivalents of base were used in the neutralization of hydrochloride salt. Aminopyrazole **5** also formed the corresponding pyrazolotriazine under diazotization conditions expanding the application of the methodology here described.

4. Experimental section

General: NMR spectra were recorded with Bruker AC 200 and 400 spectrometers. Chemical shifts are reported in ppm relative to internal TMS. All chemicals were of reagent grade and used without purification. High-resolution mass spectra were recorded with an Agilent LCTOF instrument. Column chromatography was carried out on grade 60 silica gel (70–230). Compounds **3a–d** were prepared from monosubstituted hydrazine (**3a**), monosubstituted hydrazine hydrochlorides (**3b** and **3c**), or monosubstituted hydrazine dihydrochloride (**3d**) and ethoxymethylenemalononitrile, by the methodology described in the literature.[11]

Compounds **4a–c** and their precursors were synthesized by methodologies described in the literature.[19]

Acknowledgments

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Supplementary data

Supplementary data (experimental procedure and analyzes data of compounds **1b–d**, **2a–c**, **3b–d**, **4a–c**, **5**, **9a–d, 10a–d, 11a**, **11d** and **12** are presented) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.040.

References and notes

1. Kelley, J.; Wilson, D.; Styles, V.; Soroko, F.; Cooper, B. *J. Heterocycl. Chem.* **1995**, *32*, 1417–1421.
2. Simons, C. In *Nucleoside Mimetics: Their Chemistry and Biological Properties (Advanced Chemistry Texts)*; Gordon and Breach Science Publishers: Amsterdam, 2001; Vol. 4, pp 83–102 and references cited therein.
3. Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269–286.
4. Woolley, D.; Shaw, E. *J. Biol. Chem.* **1951**, *189*, 401–410.
5. De Clercq, E. *Nat. Rev. Drug Discovery* **2002**, *1*, 13–25.
6. Seela, F.; Lindner, M.; Glaçon, V.; Lin, W. *J. Org. Chem.* **2004**, *69*, 4695–4700.
7. Kelly, J.; Wilson, D.; Styles, V.; Soroko, H.; Hunt, J.; Briggs, E.; Clarke, E.; Whittingham, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5222–5226.
8. Migawa, M.; Townsend, L. *J. Org. Chem.* **2001**, *66*, 4776–4782.
9. Migawa, M.; Drach, J.; Townsend, L. *J. Med. Chem.* **2005**, *48*, 3840–3851.
10. (a) Montgomery, J.; Laseter, A.; Shortnacy, A.; Clayton, S.; Thomas, H. *J. Med. Chem.* **1975**, *18*, 564–567; (b) Li, H.; Zhu, Y.; Song, X.; Hu, F.; Liu, B.; Li, Y.; Niu, Z.; Liu, P.; Wang, Z.; Song, H.; Zou, X.; Yang, H. *J. Agric. Food. Chem.* **2008**, *56*, 9535–9542; (c) Harb, A.; Abbas, H.; Mostafa, F. *J. Iranian Chem. Soc.* **2005**, *2*, 115–123; (d) Dawood, K.; Farag, A.; Khedr, N. *Arkivoc* **2008**, *XV*, 166–175; (e) Andersen, K.; Pedersen, E. *Liebigs Ann. Chem.* **1986**, 1012–1020; (f) Sugiyama, T.; Schweinberger, E.; Kazimierczuk, Z.; Ramzaeva, N.; Rosemeyer, H.; Seela, F. *Chem. Eur. J.* **2000**, *6*, 369–378.
11. Moyano, E.; Colomer, J.; Yranzo, G. *Eur. J. Org. Chem.* **2008**, *19*, 3377–3381.
12. Cheng, C.; Robins, R. *J. Org. Chem.* **1956**, *21*, 1240–1256.
13. Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A., Rees, C., Scriven, E., Eds.; Elsevier, 1996; Vol. 3.01, pp 1–75. and references cited herein.
14. López Rivilli, M.; Moyano, E.; Yranzo, G. *Tetrahedron Lett.* **2010**, *51*, 478–481.
15. Kelley, J.; Davis, R.; McLean, E.; Glen, R.; Soroko, F.; Cooper, B. *J. Med. Chem.* **1995**, *38*, 3884–3888.
16. General procedure for diazotization of aminopyrazoles **1a–d** and aminoimidazoles **2a–c**: Aqueous $NaNO_2$ (1.8 mmol, 1 mL) was added to a well-stirred and cooled solution (0–5 °C) of pyrazole or imidazole (1 mmol) in a mixture of HCl/AcOH (3:1, 20 mL) over a period of 10 min. The reaction mixture was allowed to warm at room temperature and was stirred for 20 h.

The precipitate of pyrazolotriazinone or imidazotriazinone was then filtered off, and the residue was diluted with water (20 mL), extracted with dichloromethane (3×30 mL), and dried with anhydrous $MgSO_4$. The resulting solution was concentrated to dryness, and the solid was then subject to chromatographic column separation with dichloromethane and dichloromethane/ethyl acetate in different proportions.

17. Butler, R. *Chem. Rev.* **1975**, *75*, 241–257.
18. Zollinger, H. *Acc. Chem. Res.* **1973**, *6*, 335–341.
19. Milanesi, S.; Fagnoni, M.; Albini, A. *Chem. Commun.* **2003**, 216–217.
20. (a) Alves, M.; Booth, B.; Proença, M. *J. Chem. Soc., Perkin Trans. 1.* **1990**, *6*, 1705–1990; (b) Booth, B.; Costa, F.; Mahmood, Z.; Pritchard, R.; Proença, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, *13*, 1853–1858; (c) Booth, B.; Carpenter, R.; Morlock, G.; Mahmood, Z.; Pritchard, R. *Synthesis* **2001**, *16*, 2393–2396.
21. Kirk, K.; Cohen, L. *J. Am. Chem. Soc.* **1973**, *95*, 4619–4624.