

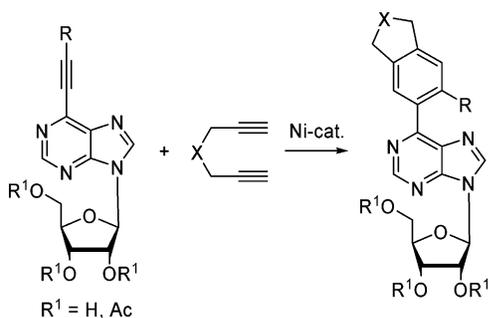
Preparation of Highly Substituted 6-Arylpurine Ribonucleosides by Ni-Catalyzed Cyclotrimerization. Scope of the Reaction

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Transition metal complex catalyzed cocyclotrimerization of protected alkyne-alkynylpurine ribonucleosides **1** with various diynes **2** gave rise to a series of 6-arylpurine nucleosides **3** that were further deprotected to free nucleosides **4**. Generally, the best yields of cyclotrimerizations were obtained with a catalytic system Ni(cod)₂/2PPh₃. On the other hand, CoBr(PPh₃)₃ proved to be a superior catalyst for cyclotrimerization of **1** with dipropargyl ether **2g**. In addition, Ni catalysis is also suitable for direct cyclotrimerization of unprotected alkyne-alkynylpurine ribonucleosides **5** to the corresponding 6-arylpurine ribonucleosides **4**.

Purine bases and nucleosides bearing an aryl moiety in position 6 display diverse types of biological activity: some substituted 6-arylpurine bases are antagonists of corticotropin releasing hormones¹ or adenosine receptors² or possess antimycobacterial and antibacterial activity,³ while 6-arylpurine

ribonucleosides show significant cytostatic⁴ and anti-HCV⁵ effects. Also, 6-alkynylpurines are potent cytostatics⁶ and inhibit 15-lipoxygenase.⁷ In addition, unnatural 6-arylpurine nucleobases were used in artificial base pairs⁸ and as covalent base-pair analogues.⁹ Until recently, biological activity screening and other applications (e.g., in chemical biology) have been limited to easily accessible purines bearing simple aryl groups, while highly substituted and/or functionalized ones still remain to be explored. Since many bulky and hydrophobic aryl C-nucleosides also have been used recently as potential nucleobase surrogates¹⁰ in extension of the genetic alphabet, the preparation of 6-arylpurines bearing bulky hydrophobic substituents is of particular interest. As for the synthetic methods, 6-arylpurines mostly have been prepared by cross-coupling reactions¹¹ of 6-halopurines with various organometallics (arylborynic acids, stannanes, or zinc halides); however, for highly functionalized aryl groups, such organometallics would not be easily available or even stable enough under the reaction conditions. Therefore, alternative procedures of their synthesis are still of interest.

In our previous reports, we have shown that cyclotrimerization of 6-alkynylpurines with zirconacyclopentadienes¹² or with α,ω -diynes catalyzed by in situ generated Ni(0)-species from NiBr₂-(dpe)/Zn is a suitable method for the preparation of 9-Bn- or 9-THP protected 6-arylpurines.¹³ Herein, we wish to describe an extension of the latter methodology to the synthesis of the corresponding ribonucleosides. It is not a routine extension because for nucleoside synthesis, the method must be compatible with acyl protected sugar moieties and with rather labile nucleosidic bonds, and also, the functionality must survive

- (3) (a) Bakkestuen, A. K.; Gundersen, L.-L.; Langli, G.; Liu, F.; Nolsøe, J. M. *J. Bioorg. Med. Chem. Lett.* **2000**, *10*, 1207–1210. (b) Andresen, G.; Gundersen, L.-L.; Nissen-Meyer, J.; Rise, F.; Spilberg, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 567–569. (c) Gundersen, L.-L.; Nissen-Meyer, J.; Spilberg, B. *J. Med. Chem.* **2002**, *45*, 1383–1386. (d) Bakkestuen, A. K.; Gundersen, L.-L.; Utenova, B. T. *J. Med. Chem.* **2005**, *48*, 2710–2723.
- (4) (a) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817–1825. (b) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2001**, *66*, 483–499.
- (5) Hocek, M.; Nauš, P.; Pohl, R.; Votruba, I.; Furman, P. A.; Tharnish, P. M.; Otto, M. *J. Med. Chem.* **2005**, *48*, 5869–5873.
- (6) (a) Hocek, M.; Votruba, I. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1055–1058. (b) Hocek, M.; Dvořáková, H.; Císařová, I. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1560–1578. (c) Hocek, M.; Votruba, I.; Dvořáková, H.; *Tetrahedron* **2003**, *59*, 607–611. (d) Hocek, M.; Štěpnička, P.; Ludvík, J.; Císařová, I.; Votruba, I.; Řeha, D.; Hobza, P. *Chem.—Eur. J.* **2004**, *10*, 2058–2066. (e) Nauš, P.; Votruba, I.; Hocek, M. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1955–1970. (f) Brathe, A.; Gundersen, L.-L.; Nissen-Meyer, J.; Rise, F.; Spilberg, B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 877–880.
- (7) Berg, T. C.; Gundersen, L.-L.; Eriksen, A. B.; Malterud, K. E. *Eur. J. Org. Chem.* **2005**, 4988–4994.
- (8) Hirao, I.; Ohtsuki, T.; Fujiwara, T.; Mitsui, T.; Yokogawa, T.; Okuni, T.; Nakayama, H.; Takio, K.; Yabuki, T.; Kigawa, T.; Kodama, K.; Yokogawa, T.; Nishikawa, K.; Yokoyama, S. *Nat. Biotechnol.* **2002**, *20*, 177–182.
- (9) Havelková, M.; Dvořák, D.; Hocek, M. *Tetrahedron* **2002**, *58*, 7431–7435.
- (10) (a) Pathak, A. K.; Pathak, V.; Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2004**, *47*, 273–276. (b) Kool, E. T. *Acc. Chem. Res.* **2002**, *35*, 936–943. (c) Kool, E. T.; Morales, J. C.; Guckian, K. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 990–1009.
- (11) Review: Hocek, M. *Eur. J. Org. Chem.* **2003**, 245–254.
- (12) For Ni-mediated reaction of 6-alkynylpurines with zirconacyclopentadienes, see: Turek, P.; Kotora, M.; Hocek, M.; Votruba, I. *Collect. Czech. Chem. Commun.* **2005**, *70*, 339–349.
- (13) (a) Turek, P.; Kotora, M.; Hocek, M.; Císařová, I. **2003**, *44*, 785–788. (b) Turek, P.; Kotora, M.; Tišlerová, I.; Hocek, M.; Votruba, I.; Císařová, I. *J. Org. Chem.* **2004**, *69*, 9224–9233.

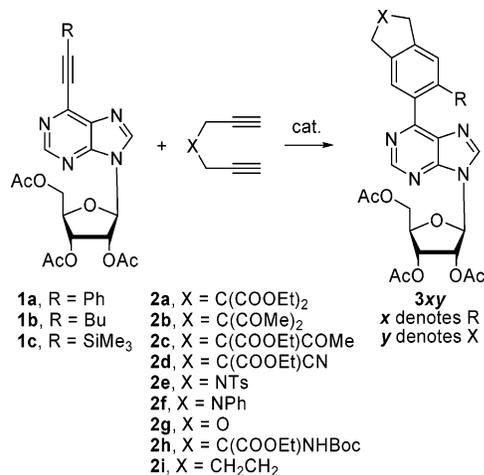
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(1) Cocuzza, A. J.; Chidester, D. R.; Culp, S.; Fitzgerald, L.; Gilligan, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1063–1066.

(2) Chang, L. C. W.; Spanjersberg, R. F.; von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Brussee, J.; Izerman, A. P. *J. Med. Chem.* **2006**, *49*, 2861–2867.

SCHEME 1. Cyclotrimerization of Alkynylpurine Nucleosides **1 with Diynes **2****


deprotection. This paper then reports on an efficient and modular synthesis of highly substituted 6-aryluracil ribonucleosides by Ni catalyzed cyclotrimerizations of 6-ethynylpurines **1** with α,ω -diynes **2** (Scheme 1). In addition, a comparison of two Ni catalytic systems, NiBr₂(dppe)/Zn and Ni(cod)₂/2PPh₃, and in some cases also a Co catalyst, is given.

Since Ni(cod)₂/2PPh₃^{14–16} and other Ni based systems^{17,18} are known to be efficient catalysts for the cyclotrimerization of various alkynes, it was desirable to compare their reactivity with the NiBr₂(dppe)/Zn system.^{13,19} Our initial study was focused on the reaction of **1a** with **2a** in different solvents to optimize reaction conditions. The results presented in Table 1 show that yields of the corresponding arylpurinylglycoside **3aa** rose with the increasing polarity of the solvent used. Thus, the best yield of **3aa** was obtained in MeCN (81%), which is in agreement with previous observations.

With the optimized reaction conditions in hand, we examined the cyclotrimerization of 6-phenylethynyl-**1a**, 6-butylethynyl-**1b**, and 6-[(trimethylsilyl)ethynyl]purine riboside-**1c** with various alkynes (Table 2). The reactions of **1a** catalyzed by Ni(cod)₂/2PPh₃ proceeded in good yield with **2a–2d**, **2g**, and **2h** (71–88%) (entries 1–4, 7, and 8). The cyclotrimerization with di-

TABLE 1. Influence of the Solvent on the Course of the Reaction of **1a with **2a****

entry	catalyst (20 mol %) ^a	solvent	yield (%) ^b
1	Ni(cod) ₂ /2PPh ₃	toluene	36
2	Ni(cod) ₂ /2PPh ₃	CH ₂ Cl ₂	13
3	Ni(cod) ₂ /2PPh ₃	THF	40
4	Ni(cod) ₂ /2PPh ₃	acetone	52
5	Ni(cod) ₂ /2PPh ₃	DMF	63
6	Ni(cod) ₂ /2PPh ₃	MeCN	81

^a 20 °C, 24 h. ^b Isolated yield.

propargylamines **2e** and **2f** gave the corresponding products **3ae** and **3af** in average yields of 48 and 36%, respectively (entries 5 and 6). In the case of 1,7-octadiyne, the yield of **3ai** was low (13%). On the other hand, the reaction of **1a** catalyzed by NiBr₂(dppe)/Zn provided the products in inferior yields (entries 1–4, and 7). Surprisingly, this system proved to be more efficient in the reaction with dipropargylamines **2e** and **2f**; the corresponding products **3ae** and **3af** were obtained in 70 and 69% yields, respectively (entries 5 and 6). The cyclotrimerization of **1a** with **2a** was tested also in the presence of Ni(cod)₂ and polymeric PPh₃; however, the corresponding product **3aa** was obtained only in very low yield (7%). An attempt to carry out the cyclotrimerization with CpCo(CO)₂²⁰ did not yield any product, thus confirming the previous results.^{17b} As expected, the cyclotrimerization of **1a** with dipropargyl ether **2g** was efficiently catalyzed by CoBr(PPh₃)₃^{13b,21} to furnish **3ag** in 80% yield (entry 7). Interestingly, the same catalyst was also able to cyclotrimerize dipropargylphenylamine **2f** to **3af** in 30% yield (entry 6).

The cyclotrimerizations of **1b** and **1c** with diynes **2** were carried out in a similar manner. Thus, reactions catalyzed by Ni(cod)₂/2PPh₃ proceeded in good yields only with **2a** (entries 10 and 14) giving **3ba** and **3ca** in 85 and 66%, respectively. In other cases, the yields were rather low in the range of 15–39% (entries 11, 12, 14, and 15). Again, the NiBr₂(dppe)/Zn system proved to be more efficient for the cyclotrimerization of dipropargylamine **2e** with **1c** (entry 14); the corresponding product **3ce** was obtained in higher yield (41%). The cyclotrimerizations of dipropargyl ether **2g** proceeded well in the presence of CoBr(PPh₃)₃ to give the corresponding products in 28 and 55% yield (entries 12 and 15).

In the next step, the obtained **3xy** were deprotected to obtain free 6-aryluracil ribonucleosides **4xy**. The deprotection of the triacetylriboside moiety was carried out with 20 mol % MeONa in MeOH at 20 °C within 1 h (Scheme 2). Generally, the deprotection proceeded in most cases to give expected nucleosides **4xy**, other ester or keto groups present in the starting molecules were not affected. Only the deprotection of **3ad** afforded the product **4ad** as methyl cyanoacetate (71%) instead of ethyl cyanoacetate. Very good yields of **4ac** and **4ag** (82 and 85%) were obtained in the deprotection of [acetyl-(carboxyethyl)indanyl]purine **3ac** and (dihydroisobenzofuranyl)-purine **3ag**. The deprotection of [diethylcarboxy]indanyl]purine **3aa** afforded the corresponding products **4aa** in 76% yield. In the case of tosyl derivative **3ae**, the deprotection resulted in a moderate yield of **4ae** (65%). The deprotection proceeded also with *n*-butyl and trimethylsilyl substituted derivatives **3ba** and **3ca** to afford the corresponding products **4ba** and **4ca** in 88 and 81% yield, respectively.

(20) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–556.

(21) Field, L. D.; Ward, A. J.; Turner, P. *Aust. J. Chem.* **1999**, *52*, 1085–1092.

(14) (a) Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133–6135. (b) Sato, Y.; Nishimata, T.; Mori, M. *Heterocycles* **1997**, *44*, 443–457. (c) Sato, Y.; Ohashi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5231–5234.

(15) (a) Stará, I. G.; Starý, I.; Kollárovič, A.; Teplý, F.; Vyskočil, Š.; Šaman, D. *Tetrahedron Lett.* **1999**, *40*, 1993–1996. (b) Teplý, F.; Stará, I. G.; Starý, I.; Kollárovič, A.; Šaman, D.; Rulíšek, L.; Fiedler, P. *J. Am. Chem. Soc.* **2002**, *124*, 9175–9180. (c) Stará, I. G.; Starý, I.; Kollárovič, A.; Teplý, F.; Šaman, D.; Fiedler, P. *Collect. Czech. Chem. Commun.* **2003**, *68*, 917–930. (d) Teplý, F.; Stará, I. G.; Starý, I.; Kollárovič, A.; Šaman, D.; Fiedler, P.; Vyskočil, Š. *J. Org. Chem.* **2003**, *68*, 5193–5197.

(16) (a) Hocek, M.; Stará, I. G.; Starý, I.; Dvořáková, H. *Tetrahedron Lett.* **2001**, *42*, 519–522. (b) Hocek, M.; Stará, I. G.; Starý, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1223–1235.

(17) (a) Rosenthal, U.; Schultz, W. *J. Organomet. Chem.* **1987**, *321*, 103–117. (b) Rosenthal, U.; Schultz, W. *J. Organomet. Chem.* **1988**, *348*, 135–139.

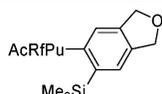
(18) For nickel-mediated cyclotrimerizations, see: (a) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans 1* **1990**, 2603–2606. (b) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Chem. Commun.* **1991**, 277–278. (c) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans 1* **1992**, 2163–2168.

(19) For application of the NiBr₂(dppe)/Zn system in other alkyne cyclotrimerizations, see: (a) Jeevanandam, A.; Korivi, R. J.; Huang, I.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 807–810. (b) Dufková, L.; Čiřarová, I.; Štěpnička, P.; Kotorá, M. *Eur. J. Org. Chem.* **2003**, 2882–2887. (c) Rodríguez, J. G.; de los Rios, C.; Lafuente, A. *Tetrahedron* **2005**, *61*, 9042–9051.

TABLE 2. Cyclotrimerization of Alkynylpurine Ribonucleosides **1** with Diynes **2**

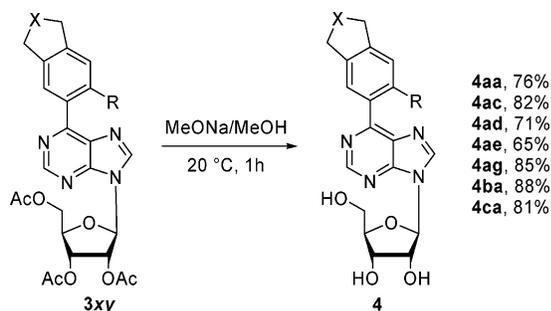
Entry	Purine	Diyne	Catalyst ^a	Product ^b	Yield (%) ^c	
1	1a	2a	Ni(cod) ₂ /2PPh ₃		3aa	81
			Ni(cod) ₂ /poly-PPh ₃		7	
			NiBr ₂ (dppe)/Zn		37	
			CpCo(CO) ₂ ^d		0	
2	2b	NiBr ₂ (dppe)/Zn		3ab	86	
				62		
3	2c	NiBr ₂ (dppe)/Zn		3ac	84	
				48		
4	2d	NiBr ₂ (dppe)/Zn		3ad	85	
				35		
5	2e	NiBr ₂ (dppe)/Zn		3ae	48	
				70		
6	2f	NiBr ₂ (dppe)/Zn		3af	36	
				CoBr(PPh ₃) ₃ ^e	69	
				30		
7	2g	NiBr ₂ (dppe)/Zn ^f		3ag	71	
				CoBr(PPh ₃) ₃	45	
				80		
8	2h	Ni(cod) ₂ /2PPh ₃		3ah	88	
9	2i	Ni(cod) ₂ /2PPh ₃ ^f		3ai	13	
10	1b	2a	NiBr ₂ (dppe)/Zn		3ba	85
					23	
11	2d	Ni(cod) ₂ /2PPh ₃		3bd	39	
12	2g	CoBr(PPh ₃) ₃ ^g		3bg	22	
				28		
13	1c	2a	NiBr ₂ (dppe)/Zn		3ca	66
					18	
14	2e	Ni(cod) ₂ /2PPh ₃ ^f		3ce	23	
			NiBr ₂ (dppe)/Zn		41	

Table 2. (Continued)

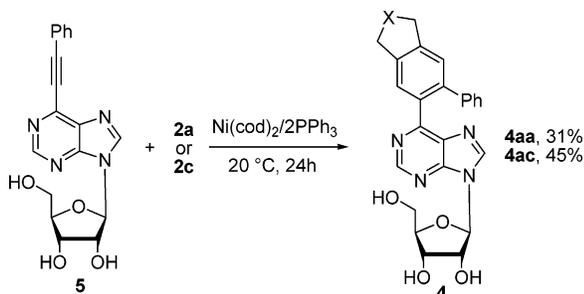
Entry	Purine	Diyne	Catalyst ^a	Product ^b	Yield (%) ^c
15		2g	Ni(cod) ₂ /2PPh ₃ ^f		15
			CoBr(PPh ₃) ₃ ^g		55

^a Reactions were carried out at 20 °C for 24 h unless otherwise noted. ^b AcRfPur = 2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl. ^c Isolated yield. ^d 140 °C. ^e 8 h. ^f 48 h. ^g 1 h.

SCHEME 2. Deprotection of Peracetylated Nucleosides 3 to Free Nucleosides 4



SCHEME 3. Cyclotrimerization of Free Purine Ribonucleoside 5 with 2



From a synthetic point of view, it is desirable to avoid deprotection and to cyclotrimerize unprotected 6-alkynylpurine ribonucleosides with diynes directly to 6-arylpurine nucleosides. Since it has been shown that the presence of free hydroxyl groups in a molecule of an alkyne did not inhibit the reaction,^{17,18,22} the unprotected 6-(phenylethynyl)purine riboside **5** was cyclotrimerized with **2a** and **2c** by a catalytic amount of Ni(cod)₂/2PPh₃ (Scheme 3). The reaction took place; however, the desired unprotected arylpurine ribosides **4aa** and **4ac** were obtained in rather mediocre yields of 31 and 45%, respectively. Obviously, these results indicate that this route is not a superior alternative to cyclotrimerization of protected nucleosides; however, it could be of some use for derivatives with functionalities incompatible with deprotection by sodium methoxide.

The cyclotrimerization approach to highly substituted 6-arylpurines previously reported¹³ only for purine bases is applicable also for an efficient synthesis of the corresponding nucleosides. From general point of view, the comparison of catalytic activity of the Ni(0)-species generated from Ni(cod)₂/2PPh₃ or NiBr₂(dppe)/Zn is clearly in favor of the former system, which is suitable for cocyclotrimerization of various 6-alkynylpurine

ribosides with a range of diynes. On the other hand, in some cases (e.g., the cyclotrimerizations with dipropargylamines), the use of the latter system was more effective. The origin of this phenomenon is not yet clear and will be the object of a future study. As for other catalysts, CoBr(PPh₃)₃ proved to be excellent for cyclotrimerization of dipropargyl ether and also showed reasonable catalytic activity for reactions with dipropargylamines. The obtained results are in accord with those reported for other 6-alkynylpurines and thus should be considered as reliable guidelines for future cyclotrimerization of other alkynylpurinyl derivatives. In addition, the cyclotrimerization could even be carried out with substrates bearing free hydroxyl groups to give the desired product in reasonable yields avoiding the protection–cyclotrimerization–deprotection reaction sequence.

Experimental Section

General Procedure for Ni(cod)₂/2PPh₃ Catalyzed Cyclotrimerization of 6-Alkynylpurines 1 with Diynes 2. Into a mixture of Ni(cod)₂ (0.04 mmol, 11 mg) and PPh₃ (0.10 mmol, 26 mg) was added a solution of 6-alkynylpurine **1** (0.20 mmol) and diyne **2** (0.22 mmol) in dry MeCN (4 mL). The reaction mixture was initially stirred at 20 °C for 24 h or until the consumption of the starting material (TLC). Then, the solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography.

6-[6-Phenyl-2,2-di(carboxyethyl)indan-5-yl]-9-(2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl)-9*H*-purine (3aa). Column chromatography on silica gel (diethyl ether) afforded 116 mg (81%) of a white foam: [α]_D –22.8 (c 0.23, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.28 (t, 6H, *J* = 7.1 Hz), 2.09, 2.10, and 2.15 (3 × s, 3 × 3H), 3.70 and 3.72 (2 × s, 2 × 2H), 4.23 (q, 4H, *J* = 7.1 Hz), 4.36 (dd, 1H, *J* = 13.1, 5.3 Hz), 4.43–4.49 (m, 2H), 5.67 (t, 1H, *J* = 5.3, 4.9 Hz), 5.90 (t, 1H, *J* = 5.3, 5.0 Hz), 6.19 (d, 1H, *J* = 5.0 Hz), 7.12 (m, 5H), 7.38 (s, 1H), 7.60 (s, 1H), 8.03 (s, 1H), 8.83 (s, 1H); ¹³C NMR (125.8 MHz, CDCl₃) δ 14.0, 20.4, 20.5, 20.7, 40.2, 40.4, 60.6, 61.8, 62.9, 70.5, 73.15, 80.3, 86.4, 126.5, 126.7, 126.7, 127.8, 129.2, 132.8, 133.1, 139.4, 141.2, 141.2, 142.4, 142.5, 150.9, 152.4, 159.8, 169.3, 169.5, 170.3, 172.4; IR (CHCl₃) ν 3031, 2986, 1750, 1732, 1588, 1369, 1248, 1097, 1069, 1052 cm^{–1}; MS (FAB, *m/z* (rel. %)) 715 (M⁺ + H, 5), 457 (15), 139 (76), 97 (100); HR–MS (FAB) calcd for C₃₇H₃₈N₄O₁₁ [M⁺ + H] 715.2615, found 715.2632. EA calcd for C₃₇H₃₈N₄O₁₁: C 62.18, H 5.36, N 7.84; found: C 61.88, H 5.34, N 7.58. *R*_f (1:4 hexane/EtOAc) = 0.45.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) (a) Bicev, P.; Furlani, A.; Sartori, G. *Gazz. Chim. Ital.* **1973**, *103*, 849–858. (b) Bicev, P.; Furlani, A.; Russo, M. V. *Gazz. Chim. Ital.* **1980**, *110*, 25–29.